

Facial Emotion Processing in Schizophrenia: A Meta-analysis of Functional Neuroimaging Data

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Background: People with schizophrenia have difficulty with emotion perception. Functional imaging studies indicate regional brain activation abnormalities in patients with schizophrenia when processing facial emotion. However, findings have not been entirely consistent across different studies. **Methods:** Activation likelihood estimation (ALE) meta-analyses were conducted to examine brain activation during facial emotion processing in patients with schizophrenia, controls, and patients compared with controls. Secondary meta-analyses were performed to assess the contribution of task design and illness chronicity to the results reported. **Results:** When processing facial expressions of emotions, both patients with schizophrenia and healthy controls activated the bilateral amygdala and right fusiform gyri. However, the extent of activation in these regions was generally much more limited in the schizophrenia samples. When directly compared with controls, the extent of activation in bilateral amygdala, parahippocampal gyrus and fusiform gyrus, right superior frontal gyrus, and lentiform nucleus was significantly less in patients. Patients with schizophrenia, but not controls, activated the left insula. A relative failure to recruit the amygdala in patients occurred regardless of whether the task design was explicit or implicit, while differences in fusiform activation were evident in explicit, not implicit, tasks. Restricting the analysis to patients with chronic illness did not substantially change the results. **Conclusions:** A marked underrecruitment of the amygdala, accompanied by a substantial limitation in activation throughout a ventral

temporal-basal ganglia-prefrontal cortex “social brain” system may be central to the difficulties patients experience when processing facial emotion.

Key words: meta-analysis/schizophrenia/emotion perception/amygdala

Introduction

Impaired emotion perception is a core feature of schizophrenia.^{1,2} There is a consensus that patients with schizophrenia have difficulties in perceiving and expressing facial emotional expression. General processing of positive and negative expressions in schizophrenia appears to be differentially altered,² and patients with schizophrenia may be particularly sensitive to unpleasant emotional content.^{2–5} Functional imaging has recently allowed this important aspect of schizophrenia to be examined. Activation abnormalities during facial emotion perception in limbic and paralimbic regions have been reported.^{6,7} However, the literature is not always consistent, and interpretation is complicated by the range of experimental designs and differences in the clinical characteristics of the patient samples recruited.

Empirical evidence suggests that several brain regions could be involved in emotional perception in schizophrenia. The amygdala is critical to fundamental experience of emotional stimuli, and findings from animal studies⁸ and neurological patients⁹ are in agreement. Structural imaging suggests that patients with schizophrenia have smaller amygdala volumes than healthy controls,¹⁰ and functional imaging data record abnormalities of amygdala activation during different aspects of emotion processing in schizophrenia. Studies indicate that, compared with healthy controls, patients with schizophrenia and their nonpsychotic siblings fail to activate bilateral amygdala regions during induction of sad mood.^{11,12} Lower bilateral amygdala activation in patients relative to healthy controls has been reported during a facial identification task¹³ and in an emotional valence and facial discrimination task.^{6,14}

However, findings relating to amygdala activation in schizophrenia have not always been consistent. While some researchers found bilateral amygdala activation in

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healthy controls but not schizophrenic patients during facial emotion identification and intensity tasks,^{13,15} others observed these abnormalities only in paranoid patients.¹⁶ A number of studies have reported that patients with schizophrenia show reduced activation in the left amygdala,^{6,17,18} in contrast with those that found reduced activation in the right amygdala.^{14,19} Moreover, several studies have reported enhanced activity in the amygdala in schizophrenia during the presentation of facial emotional expressions.^{20–23}

As a repository for long-term memories, the hippocampus could be considered a resource for referencing or placing emotions in the context of previous experiences. Patients with schizophrenia showed reduced activation of the bilateral hippocampus during facial emotion discrimination compared with healthy controls.⁶ Several more recent studies are also consistent with underactivation of the hippocampus in patients with schizophrenia during facial emotion perception tasks.^{18,19,24} In contrast, increased hippocampus activation was found in a subgroup of nonparanoid patients.¹⁶ Similarly, researchers reported greater medial temporal lobe activation in patients with schizophrenia during passive viewing of emotional faces and sustained activity in the hippocampus in response to fearful faces.^{20,25}

There are also inconsistencies surrounding the nature of fusiform gyrus involvement in emotion perception in schizophrenia. When patients performed a facial emotion discrimination and identification task, their bilateral fusiform gyri were not activated, while the controls showed the expected activation in response to faces in right lateral fusiform gyrus.²⁶ Moreover, underactivity in the right fusiform region was found in patients during remission.¹⁴ Unlike these studies, greater activation in schizophrenia has been observed in bilateral fusiform gyri during the presentation of neutral faces.²⁷

These temporal lobe regions are postulated to modulate the activity of the prefrontal cortex during facial emotion processing through extensive reciprocal connections.⁹ The orbitofrontal cortex (OFC) forms an interface between emotion and cognition²⁸ and, together with the middle temporal lobe, precuneus, and posterior cingulate, is implicated in making social judgments and empathy.²⁹ In addition, the medial prefrontal cortex (MPFC) permits an understanding of the mental state of others or theory of mind.^{30,31} Some researchers have reported stable hypoactivations in patients in the OFC during facial emotion perception,²⁴ while others observed reduced activation in MPFC when viewing negative emotional stimuli.^{19,32} On the other hand, greater activation in MPFC for aversive compared with nonaversive stimuli has been recorded in patients with schizophrenia.¹⁵

What is needed is a meta-analytical approach to synthesize these important datasets and help resolve the neural basis of facial emotional perception in patients with schizophrenia with reference to healthy volunteers. Therefore, we aimed to make an objective, systematic,

and quantitative analysis of the literature pertaining to perception of facial expression of emotion in schizophrenia. We adopted a relatively recent voxelwise technique, activation likelihood estimation (ALE).^{33,34} This technique can accommodate the large amounts of data generated across multiple neuroimaging studies and map the involvement of sublobar components of brain with good spatial resolution. The output identifies brain areas most consistently replicated thereby reducing the chances of false-positive findings.

Methods

Literature Search

We performed a 2-stage literature search for this meta-analysis. First, an online PsycINFO, Medline database search was conducted for the period between 1990 and October 2008; “in press” articles were also included. Search terms included “emotion,” “emotional,” “affective,” “affect,” and “facial,” with different combinations of “schizotypal,” “schizotype,” “psychosis,” “schizophrenia,” “schizo-affective disorder” and “Magnetic Resonance” or “MR” or “MRI” or “fMRI” or “neuroimaging.” The search was limited to peer-reviewed articles in English. Second, the reference lists of published articles were scrutinized for studies not indexed in the electronic databases.

Study Selection

We adopted the following inclusion criteria for the current study.

1. Studies must include patients with schizophrenia and healthy control subjects.
2. The studies had to have focused on facial emotion perception tasks and could include either active (emotion/facial discrimination or identification) and/or passive (mood induction, viewing facial emotion pictures) emotion perception tasks. Those that adopted the International Affective Picture System³⁵ were excluded because not all the pictures are of facial emotion. The stimuli had to have been presented visually, and studies with auditory stimuli were excluded.
3. The studies had to have used blood oxygenation level-dependent functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) techniques.
4. The studies had to have provided standard Talairach³⁶ or Montreal Neurologic Institute (MNI) coordinates, necessary for a voxel-level quantitative meta-analysis.^{37,38}

Studies Included in the Meta-analysis

Seventeen articles met inclusion criteria (table 1). Of these articles, 15 articles reported coordinates from

Table 1. Neuroimaging Studies of Emotion Recognition in Schizophrenia

Author, Year	Patients		Healthy Controls		Typical/ Atypical	Scanning Task	Healthy Only	Schizophrenia Only	Healthy > Schizophrenia	Schizophrenia > Healthy
	Age (y)	N	Age (y)	N						
Das et al, 2007 ³⁹	20.4	14	23.1	14	Atypical	Viewing			✓	✓
Gur et al, 2002 ⁶	28.8	14	27.4	14	Mixed	Valence, age detection	✓	✓		
Gur et al, 2007 ⁷	30.1	16	25.0	17	Mixed	Facial identification	✓	✓	✓	
Habel et al, 2004 ¹²	32.8	13	33.4	26	Mixed	Viewing			✓	
Hall et al, 2008 ⁴⁰	37.7	19	35.1	24	Mixed	Gender decision			✓	
Hempel et al, 2003 ¹³	26.0	9	28.0	10	Atypical	Facial discrimination/ facial identification			✓	✓
Holt et al, 2005 ²⁵	45.4	18	43.9	16	Mixed	Viewing	✓		✓	✓
Holt et al, 2006 ²⁰	47.7	15	48.2	16	Mixed	Viewing	✓	✓		✓
Johnston et al, 2005 ¹⁴	30.6	10	31.2	10	NA	Gender decision/ facial discrimination	✓	✓	✓	
Kosaka et al, 2002 ²¹	26.0	12	24.4	12	Atypical	Intensity judgment	✓	✓		✓
Michalopoulou et al, 2008 ⁴¹	35.0	11	32.0	9	Mixed	Gender decision	✓	✓	✓	
Phillips et al, 1999 ⁴²	37.0	10	30.0	5	NA	Gender decision	✓	✓	✓	
Quintana et al, 2003 ²⁶	31.3	12	26.8	12	Atypical	Facial discrimination/identity	✓	✓		
Russell et al, 2007 ¹⁶	44.7	15	35.6	10	Atypical	Gender decision			✓	✓
Surguladze et al, 2006 ²⁷	43.1	15	36.8	11	Atypical	Gender decision			✓	
Williams et al, 2004 ¹⁸	27.3	27	27.2	22	Atypical	Gender decision	✓		✓	
Williams et al, 2007 ³²	27.4	27	25.1	13	Atypical	Gender decision			✓	

patient-control contrasts, and 2 studies only reported coordinates for patients with schizophrenia and healthy controls.

As can be seen in the table 1, the scanning tasks included in the meta-analyses comprised 2 categories, explicit and implicit. The former included tasks of viewing, valence and intensity judgments, and facial discrimination and identification; the latter included tasks of gender decision, age detection, and facial identity. Some studies included both kinds of task.^{6,11,12,14,26}

Quantitative Meta-analysis Procedures

To standardize coordinates entered into the analysis, all coordinates reported in MNI were transformed to Talairach template.⁴³ Once all the coordinates were input into a text file, they were loaded into a Java-based version of GingerALE 1.2 beta software (<http://www.brainmap.org>) developed at the Research Imaging Center of Texas and analyzed step by step.

The ALE method considers the peak coordinates reported in functional neuroimaging articles as Gaussian probability distributions around these coordinates and not single points. For detailed description of the ALE method, please see studies of Laird *et al.*,³⁴ Laird *et al.*,³⁷ and Turkeltaub *et al.*³⁸

The ALE maps were created using a 6-mm full-width half-maximum (FWHM) Gaussian function to model each coordinate.³⁸ Statistical significance was determined using a permutation test of randomly distributed foci. We computed 5000 permutations using the 6-mm FWHM value, and the same number of foci was used to compute the ALE values. The final ALE maps had a threshold at $P < .01$ and were corrected for multiple comparisons using the false discovery rate method.^{34,44} Clusters were required to exceed 200 mm³ in volume. With the recently upgraded software, we could also see how many foci contributed to a given cluster. Although the explanation of the results depends on the size of meta-analysis and there are no community-accepted criteria for the results, generally speaking for a study of this size, if 6 or more foci contribute to a cluster, it is considered very robust, and if 3–5 foci contribute to a cluster, it is acceptable. It is not convincing if only 1 or 2 foci contribute to a cluster (see the forum of GingerALE, <http://www.brainmap.org/forum/>).

There are 2 methods to compare the activations between patients with schizophrenia and healthy controls. For the studies that provided direct between-group contrasts, we did 2 separate meta-analyses. For “controls > schizophrenia,” we incorporated all the coordinates activated more in healthy controls than patients with schizophrenia; for “schizophrenia > controls,” we incorporated all the coordinates activated more in schizophrenia compared with controls. Where studies did not report between-group contrast coordinates, but did provide

separate coordinates for controls and schizophrenia, we extracted the coordinates for controls alone and patients alone and then did a subtraction between the 2 groups in addition to separate meta-analysis of healthy controls alone and patients alone. The subtraction meta-analysis yields an ALE map showing regions in which the 2 groups of foci are significantly different.³⁴

Finally, to understand to what extent the task design or illness duration influenced the results, we conducted separate sub meta-analyses of results from studies using explicit tasks and implicit tasks and examined samples of chronically ill patients only.

Whole-brain maps of the ALE values were imported into MRICron software program (www.sph.sc.edu/comd/rorden/mricron) and overlaid onto the brain template for presentation purposes.

Results

Healthy Comparison Subjects Alone

Ten articles reported activations for matched healthy control subjects alone, resulting in 127 total foci. ALE images are presented in figure 1, and the ALE scores and cluster sizes for these locations are listed in table 2. The healthy controls activated 6 clusters. These regions included large portions of the bilateral fusiform gyri (3 were located in the right fusiform gyrus, and 1 was located in the left fusiform gyrus), left parahippocampal gyrus/amygdala (extending to subcallosal gyrus), and right lentiform nucleus (extending to right parahippocampal gyrus/amygdala).

Patients With Schizophrenia Alone

Eight articles reported activation for patients with schizophrenia alone, resulting in 52 foci. The ALE images, ALE scores, and cluster sizes are presented in figure 1 and table 2. The results demonstrated that the patients with schizophrenia activated some similar locations to controls, including the bilateral parahippocampal/amygdala and right fusiform gyrus, though the activation pattern was much more restricted in extent. Absent from the results of the controls-alone analysis, analysis of schizophrenia samples alone indicated activation of left insula, and 3 foci contributed to this cluster.

Healthy Controls > Patients With Schizophrenia

Thirteen articles reported a total of 70 foci of relative increases in activation in healthy control subjects compared with patients with schizophrenia while performing an emotion perception task during functional neuroimaging. ALE images, ALE scores, and cluster sizes are presented in figure 1 and table 3. Four clusters were activated more in the healthy controls compared with patients with schizophrenia. They were bilateral parahippocampal gyrus/amygdala, right superior frontal gyrus

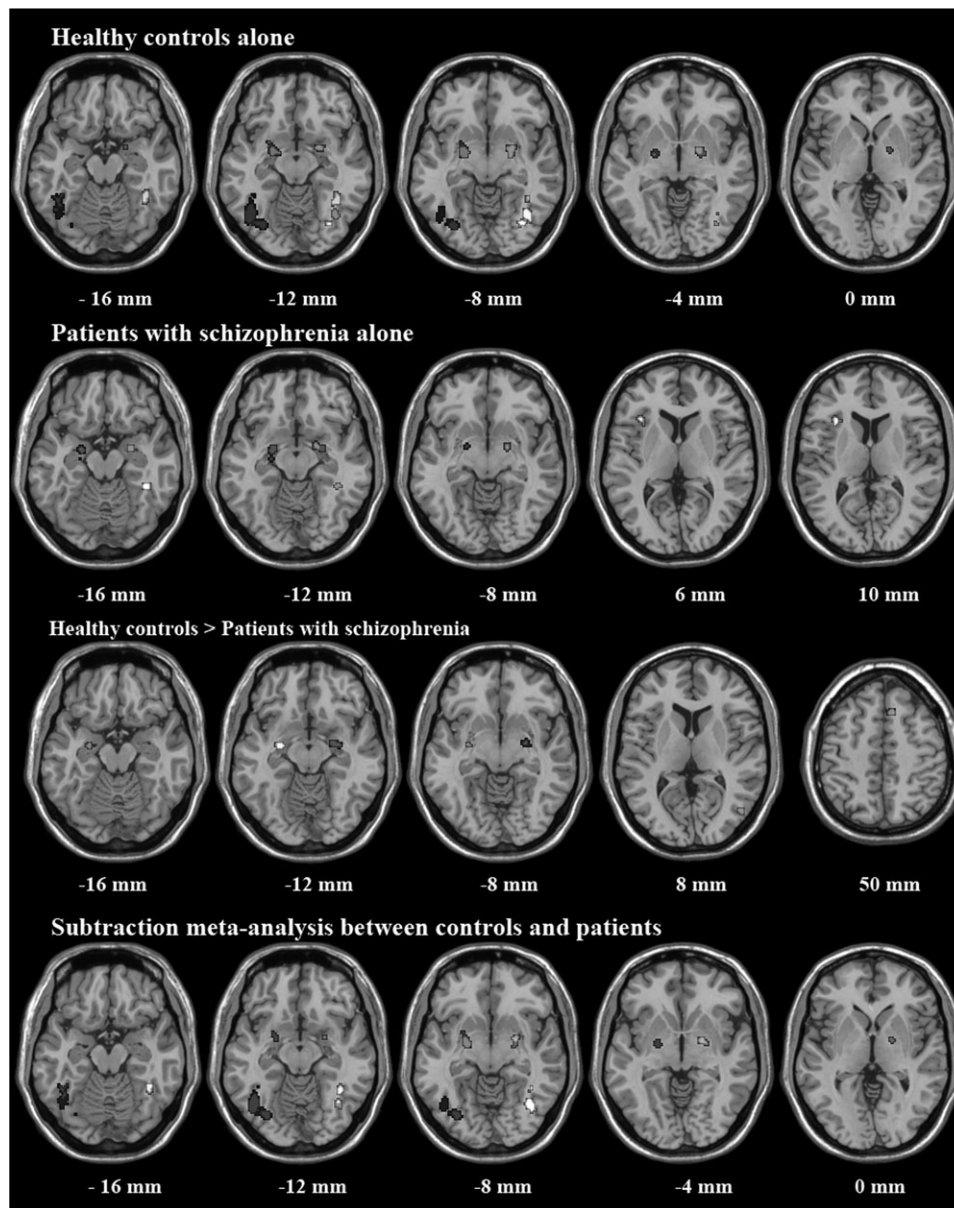


Fig. 1. Meta-analytic Activation Maps for Healthy Subjects Recruited as Controls in Facial Emotional Neuroimaging Studies (Healthy Controls), Activation Foci for Patients With Schizophrenia Alone (Patients With Schizophrenia), Activation Foci for Contrasts of Healthy Comparison Subjects Greater Than Patients (Healthy > Patients), and the Subtraction Meta-analysis Between the 2 Groups. The right side of each section represents the right side of the brain; the z-coordinate in Talairach space is indicated below each section.

(Brodmann area [BA] 6), and right middle occipital gyrus (BA 19). However, because only 2 foci contributed to this latter cluster, it may not be very reliable.

Patients With Schizophrenia > Healthy Controls

Six articles reported a total of 16 foci showing relative increases in activation in patients with schizophrenia compared with the healthy controls. Unfortunately, this number of foci is rather small, and no significant clusters survived a fairly stringent 5000 permutations and a conservative threshold of $P < .01$. Even with a looser threshold of $P < .05$, there were 16 clusters in the resul-

tant map, with only one foci contributing to each cluster. Therefore, this result is not reported further.

Subtraction Meta-analysis Between Healthy Controls and Patients With Schizophrenia

Subtraction meta-analysis between the 2 groups was also analyzed, the ALE images were presented in figure 1, and the ALE scores and cluster sizes for these locations were listed in table 3. All the ALE values were positive, indicating that the clusters in healthy controls were significantly larger than the patients. The largest cluster was centered on the left fusiform gyrus, extending to BA

Table 2. Meta-analyses of Healthy Controls Alone and Schizophrenia Patients Alone

Anatomical Region	Brodmann Area	Center			Maximum ALE Value	Volume (mm ³)	Number of Foci Contributing
		x	y	z			
Healthy controls alone							
L fusiform gyrus	19/37	-38	-66	-13	0.100	2048	21
L parahippocampal gyrus/amygdala		-21	-5	-10	0.102	784	8
R lentiform nucleus		23	-4	-8	0.062	728	8
R fusiform gyrus	37	40	-47	-15	0.069	672	8
R fusiform gyrus	19	39	-65	-10	0.097	416	5
R fusiform gyrus	19	34	-73	-10	0.046	208	3
Schizophrenia patients alone							
L parahippocampal gyrus/amygdala		-21	-8	-14	0.068	480	5
R parahippocampal gyrus/amygdala		23	-5	-14	0.061	424	4
L insula	6	-32	20	8	0.035	312	3
R fusiform gyrus	37	40	-42	-16	0.053	208	2

Note: ALE, activation likelihood estimation; L, left; R, right.

19 and BA 37; the left cerebellum was also included in this cluster. The second largest cluster was centered in the left parahippocampal gyrus/amygdala and extended to the left subcallosal gyrus. The right lentiform nucleus was at the center of a cluster that extended to the right parahippocampal gyrus/amygdala. The remaining 2 clusters were both located in the right fusiform gyrus.

Chronic Schizophrenia

Of the studies included in the meta-analysis, almost all the patients with schizophrenia were on medication, and only 5 patients in one study were medication free.³⁹ In terms of the mean duration of illness, only 2 studies included patients ill for less than 24 months.^{13,39} Therefore, there were insufficient studies to include in a meta-analysis of emotion perception in first-episode schizophrenia. How-

ever, we found that 10 studies and 50 foci could be included in a meta-analysis of “healthy controls > chronic schizophrenia,” although only 4 studies and 5 foci could be found for “chronic schizophrenia > healthy controls,” too few to do a meta-analysis. There were also too few studies reporting healthy controls and chronic patients separately. In a meta-analysis of healthy controls > chronic schizophrenia, the results were almost the same as the results from the full meta-analysis reported above, except that the right middle occipital gyrus was not part of the resultant map.

Between-Group Comparisons in the Explicit/Implicit Emotional Tasks

Explicit and implicit emotional tasks may have differentially affected brain activity.^{45,46} Therefore, we analyzed explicit and implicit emotional tasks separately.

Table 3. Comparisons Between Healthy Controls and Patients With Schizophrenia

Anatomical Region	Brodmann Area	Center			Maximum ALE Value	Volume (mm ³)	Number of Contributed Foci
		x	y	z			
Healthy controls > patients with schizophrenia							
R parahippocampal gyrus/amygdala		26	-8	-12	0.052	368	4
R superior frontal gyrus	6	9	22	51	0.051	288	3
L parahippocampal gyrus/amygdala		-26	-10	-13	0.060	272	3
R middle occipital gyrus	19	48	-72	4	0.060	208	2
Subtraction meta-analysis							
L fusiform gyrus	19	-38	-66	-13	0.100	1768	19
L parahippocampal gyrus/amygdala		-22	-5	-9	0.091	464	8
R lentiform nucleus		23	-4	-7	0.062	424	7
R fusiform gyrus	19	38	-64	-10	0.097	408	6
R fusiform gyrus	37	40	-50	-15	0.065	408	5

Note: ALE, activation likelihood estimation; R, right; L, left.

Table 4. Subtraction Meta-analysis of Healthy Controls and Schizophrenia Patients for Explicit Tasks

Anatomical Region	Brodmann Area	Center			Maximum ALE Value	Volume (mm ³)	Number of Contributed Foci
		x	y	z			
L fusiform gyrus	19/37	-39	-65	-13	0.082	1840	18
R fusiform gyrus	37	40	-52	-14	0.068	472	5
R fusiform gyrus	19	38	-64	-10	0.097	432	5
L amygdala		-21	-7	-8	0.091	368	6
R lentiform nucleus		22	-3	-5	0.060	256	3

Note: ALE, activation likelihood estimation; L, left; R, right.

For explicit emotion tasks, there were 7 studies and a total of 70 foci for healthy controls, 6 studies and 41 foci for patients with schizophrenia, 5 studies and 27 foci for healthy controls > patients with schizophrenia, and 5 studies and 15 foci for patients with schizophrenia > healthy controls. The subtraction meta-analysis of healthy controls alone and patients with schizophrenia alone in explicit tasks generated an ALE map with 5 clusters (table 4). The largest cluster was centered on the left fusiform gyrus and extended to left cerebellum. Two clusters were centered on the right fusiform gyrus. One cluster localized to the left amygdala and 1 to the right lentiform nucleus. Due to the small number of foci, the comparison of healthy controls > patients with schizophrenia and patients with schizophrenia > healthy controls did not generate meaningful results.

For implicit emotion tasks, there were 4 studies and 57 foci reported for healthy controls, 3 studies and 20 foci for patients with schizophrenia, 9 studies and 51 foci for healthy controls > patients with schizophrenia, and 1 study and 1 focus for patients with schizophrenia > healthy controls. Thus, only a healthy controls > patients with schizophrenia meta-analysis was possible, and this generated an ALE map with 4 clusters (table 5). The first cluster centered on the right superior frontal gyrus. The second and third clusters centered on the left parahippocampal gyrus/amygdala and right parahippocampal gyrus/amygdala, respectively, and the last cluster cen-

tered on the right middle occipital gyrus. Only 2 foci contributed to the last cluster, so this was not a confident finding.

Discussion

ALE meta-analyses showed that when processing facial expressions of emotions, patients with schizophrenia activated some similar regions as controls, namely, the bilateral parahippocampal/amygdala and right fusiform gyrus. However, the extent of activation in these regions was generally much more limited in the schizophrenia samples. When directly compared with controls, activation in bilateral parahippocampal gyrus/amygdala, bilateral fusiform gyrus, right superior frontal gyrus, and right lentiform nucleus was significantly less extensive in patients.

Healthy Controls Alone

ALE meta-analysis of the healthy controls during emotion perception indicated that bilateral fusiform gyrus, bilateral parahippocampal gyrus/amygdala, and right lentiform nucleus were activated. These results partly align with those reported in a meta-analytical review of 55 PET and fMRI activation studies.⁴⁷ That study found that healthy volunteers activated the medial prefrontal cortex, amygdala, cingulate, and insula in

Table 5. Healthy Controls > Patients With Schizophrenia for Implicit Tasks

Anatomical Region	Brodmann Area	Center			Maximum ALE Value	Volume (mm ³)	Number of Contributed Foci
		x	y	z			
R superior frontal gyrus	6	10	22	50	0.051	312	3
L parahippocampal gyrus/amygdala		-26	-10	-14	0.060	280	3
R L parahippocampal gyrus/amygdala		24	-8	-12	0.051	280	3
R middle occipital gyrus	19	48	-72	4	0.060	216	2

Note: ALE, activation likelihood estimation; R, right; L, left.

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response to emotion content. However, compared with the review summary,⁴⁷ we found that healthy controls also activated the bilateral fusiform gyri and right parahippocampal gyrus. There are a number of possible explanations for the differences in our studies. First, our methods were quite different from the conventional label-based meta-analysis approach.⁴⁷ Typically, the label-based meta-analysis approach is not quantitative, and it merges nonsignificant results to test for significance with pooled data. The present ALE meta-analysis method is quantitative but is mainly concerned with significant results,³⁷ and this may have contributed to the slightly different pattern of results. Second, it is likely that restricting our analyses to facial stimuli explains the strong activation pattern in the fusiform areas here, given the highly specialized role of the right fusiform for face processing in man.^{48–50} In addition, the conventional study incorporated several subsidiary meta-analyses based on the valence of emotion, the induction methods used (visual, auditory, recall/imagery), and the cognitive demands of the tasks employed.⁴⁷ In our analyses, we focused on studies using visual presentation of faces. Due to the small number of neuroimaging articles examining both schizophrenia and healthy subjects together, we were limited to a meta-analysis pooling multiple valence and cognitive conditions.

Patients With Schizophrenia Alone

Several brain areas activated in the healthy control samples were also activated in patients with schizophrenia. Activation in the amygdala, a key node in emotion processing, was recorded in the patient-alone analysis, although the cluster was limited to about half the extent of that generated in the control-alone analysis. More striking was the limitation in fusiform activation in the patient-alone analysis. As figure 1 shows, there was a near absence of ventral temporal activation in the “schizophrenia-alone” condition. Looking at table 2, separately 21 and 16 foci contributed to the left and right fusiform gyrus in healthy controls; however, only 2 foci contributed to the right fusiform gyrus in patients. While it is well accepted that higher levels of facial processing, such as emotion expression, are disrupted by schizophrenia, it has been less certain whether the normal rapid and innately human assessment of a face is affected. The minimal fusiform activation in schizophrenia samples revealed by our meta-analysis suggests that a very fundamental element of face processing may be impaired in schizophrenia. A recent study that managed to isolate face detection from other aspects of face recognition found a basic face detection deficit in schizophrenia.⁵¹ Together, our results imply that the difficulty people with schizophrenia have decoding emotional content may at least partly result from an inability to recruit the usual neural systems for face perception. Consistent with this, researchers have

shown early abnormalities in the encoding of facial features that precede the event-related potentials responses linked to recognition of facial emotion.⁵² Their work therefore adds to the evidence that impaired processing of facial emotion expression in schizophrenia may be secondary to a basic and early developmental deficit encoding faces.

In the schizophrenia-alone analysis, the results indicated clusters in similar locations, if smaller volumes, compared with the healthy subjects-alone analysis. The implication may be that when patients with schizophrenia assess facial expressions of emotion, they depend to a degree on the same series of core areas used by healthy controls. The most noticeable exception to this was activation of left insula found in schizophrenia samples but not in the healthy subjects. The insula is now recognized to play an important role in the regulation of emotion.⁵³ It projects to both the amygdala and the prefrontal cortex and is thought to be a crucial part of the neural system specialized to decode emotions from facial expressions.⁵⁴ In the context of sensitivity to unpleasant stimuli, significant insula activation here is particularly interesting because it has been strongly associated with processing disgust^{55,56} and, as mentioned previously, patients with schizophrenia have been reported to be especially sensitive to unpleasant stimuli.^{2–5} However, given that only 3 foci contributed to this result, these findings should be regarded as preliminary.

Comparisons Between Healthy Controls and Patients With Schizophrenia

Compared with healthy controls, patients with schizophrenia had a general pattern of less activation in bilateral parahippocampal gyrus/amygdala and fusiform gyrus, right superior frontal gyrus, and right lentiform nucleus. At the most simple level of interpretation, this pattern of results suggests that patients with schizophrenia have impairments in emotion processing because the extent to which they recruit brain structures usually involved in emotion is limited compared with controls.

Research on animal models has found that there are specialized subcortical pathways that allow for the early detection of emotion. Subcortical structures such as amygdala may perceive potential threat and modulate processing in early visual regions.⁵⁷ There is some evidence that this pathway also exists in humans.⁵⁸ Studies from cognitive neuroscience also confirm that the amygdala is a key region in the human brain that, together with the orbital and medial prefrontal cortex, moderates the influence of emotion on decisions.⁵⁹ The ALE meta-analysis represents converging coordinates, and because of the proximity of amygdala and hippocampus, it is difficult to establish the extent of difference in hippocampal involvement captured during facial emotion perception tasks. Researchers have observed concurrently enhanced activity of amygdala and hippocampus during the

emotional memory encoding,⁶⁰ and a functional interaction between these 2 regions has been observed during retrieval of emotional memory.⁶¹ Moreover, structural imaging studies point to a reduced volume of the hippocampus and amygdala complex in patients with schizophrenia.⁶² Thus, the failure to activate this medial temporal brain region may lead to difficulties judging the emotional significance of stimuli, a problem that is compounded when higher order cortical targets of the amygdala/hippocampal cortex do not receive accurate information to evaluate and respond to.^{63,64}

Taken together, the sparse activation of the amygdala, fusiform gyri, basal ganglia, and prefrontal lobe regions in schizophrenia, compared with controls, points to disruption across “an integrated social cognitive network.”⁶⁵ However, a note of caution is that ALE meta-analysis does not take account of the heterogeneity in studies incorporated in the analyses. Though the majority of studies reported that healthy controls activated the amygdala more than patients, there were still a few studies that reported that patients with schizophrenia recruited the right amygdala more than controls.^{20,21}

Secondary Meta-analyses

In the present study, where possible, we carried out some secondary meta-analyses. Only 2 studies examined patients in the early phase of illness,^{13,39} so we repeated a meta-analysis after excluding the 2 studies. The results were almost the same as the previous full contrast of healthy controls > patients with schizophrenia. It was not possible to fully fractionate the influence of cognitive demands on emotion processes, but this is a very important concern.⁶⁶ However, we did subanalyze the results obtained from explicit and implicit emotional tasks. In both the implicit and explicit tasks meta-analyses, patients with schizophrenia had lower activation in the bilateral parahippocampal/amygdala than controls. The fusiform gyrus was activated less in patients than controls in explicit and not implicit tasks. Thus, activation of the amygdala during both task conditions confirms a central role for the amygdala in emotion processing in controls, and a relative failure to activate the amygdala in either task condition is underlined in the patient groups. In contrast, in an explicit task, participants have to actively scrutinize faces, and inefficient facial processing in schizophrenia⁵¹ might be explained by a failure to recruit the fusiform gyri, a specialized region for facial processing.^{48,50}

In the present study, the brain regions underrecruited during face emotion perception in patients with schizophrenia, including amygdala, hippocampus, fusiform gyrus, superior frontal gyrus, and lentiform nucleus, work within a spatially and temporally defined circuitry to facilitate social functioning.^{45–47,49,53,54} This indicates that disruption at systems level, rather than discrete loci, may

best explain the pattern of activation anomaly in schizophrenia. Several studies have considered functional connectivity in patients with schizophrenia during facial emotional perception. In a fear perception task, researchers found functional disconnection in autonomic and central systems in patients with paranoid schizophrenia.¹⁸ In the same fear detection task, others found that patients with schizophrenia had disconnections in a visual-amygdala-prefrontal system,⁶⁷ and it has been suggested that basic visual-temporal dysfunction in schizophrenia may explain maladaptive appraisal of threat by people with schizophrenia.⁶⁸ Taken together, a possible lack of coordination in the orienting mechanisms, perceptual processing and prefrontal regulation of fear stimuli,⁶⁷ indicates that patients' impairments could well be due to misconnectivity across brain regions.³⁹ Structural abnormalities in a neural circuit extending from limbic cortex through striatum, then thalamus, and finally reaching the prefrontal and cingulate cortex^{69–71} are consistent with this concept of a network-wide interruption of social functioning in schizophrenia.

There are several limitations to the current study. First is the heterogeneity of the studies included. Factors that could potentially influence the results vary across the different samples, such as the behavioral performance, demographic information (gender differences, age), and clinical factors, including the duration of illness, medication dosage, and the clinical symptoms. At the present, it is not possible to directly evaluate the influence of all these factors on the results. Second, the present method did not allow for weighting of the results based on the level of statistical significance reported in each study. This means that we cannot determine the relative strengths of activation differences. Third, although the quantitative meta-analytic method used here represents a significant advance for integrating functional neuroimaging data, the method remains subject to the basic limitation of literature reviews, in particular the “file drawer” problem. That is, studies with negative findings are less likely to be published and therefore cannot influence the meta-analysis. Last, due to the stringent inclusion criteria of our study, the number of articles included was not large, especially the number that included comparisons of patients with schizophrenia and healthy controls.

The ALE meta-analysis reported here confirmed significant abnormalities in the processing of facial expressions of emotion in schizophrenia. Patients with schizophrenia tend to recruit some of the same brain regions as healthy controls when looking at facial emotion, but the extent is markedly limited. Such a fundamental difficulty in social behavior in schizophrenia deserves to be examined in much greater detail, with a view to optimizing strategies for better performance in this most everyday human behavior.

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