ORIGINAL ARTICLE

Limbic Activation Associated With Misidentification of Fearful Faces and Flat Affect in Schizophrenia

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Context: Deficits in emotion processing are prominent in schizophrenia, and flat affect is resistant to treatment and portends poor outcome. Investigation of the underlying neural circuitry can elucidate affective dysfunction.

Objective: To examine the brain circuitry for facial emotion processing, dissecting response to task demands from effects of the appearance of facial expressions.

Design: A facial emotion identification task was presented during high-field (4-T) magnetic resonance imaging. Blood oxygenation level–dependent changes were contrasted for task compared with a scrambled face baseline (blocked analysis) and for the appearance of each of the following 4 target expressions compared with neutral faces (event related): happy, sad, anger, and fear.

Setting: Participants from the Schizophrenia Research Center underwent a functional magnetic resonance imaging study at the University of Pennsylvania Medical Center.

Participants: Patients with *DSM-IV*–defined schizophrenia (n=16) and healthy controls (n=17) were recruited from the community.

Main Outcome Measures: The percentage of signal change for each contrast and performance and clinical symptom severity ratings.

Results: Patients showed reduced limbic activation compared with controls for the emotion identification task. However, event-related analysis revealed that whereas in controls greater amygdala activation was associated with correct identifications of threat-related (anger and fear) expressions, patients showed the opposite effect of greater limbic activation, portending misidentifications. Furthermore, greater amygdala activation to the presentation of fearful faces was highly correlated with greater severity of flat affect.

Conclusions: Abnormal amygdala activation in schizophrenia in response to presentation of fearful faces is paradoxically associated with failure to recognize the emotion and with more severe flat affect. This finding suggests that flat affect in schizophrenia relates to overstimulation of the limbic system.

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Deficits in emotion processing in schizophrenia disrupt social functioning.[1,2] Flat affect is a cardinal symptom that particularly diminishes the ability to communicate emotions. Like other negative symptoms, it is resistant to treatment and is associated with poor functioning and outcome.[3,4] Patients have deficits in identification and expression of emotions but apparently not in reported experience.[4-7] Notably, patients with flat affect, compared with those without flat affect, have further deficits in identifying facial emotions without being more impaired cognitively, except for verbal memory.[4]

Complementing findings in patients with brain lesions[8,9] and animal paradigms,[10,11] functional magnetic resonance imaging (fMRI) studies in healthy people have helped elucidate brain systems and processes that modulate emotion. Because the face is a major conveyor of emotion, it is used extensively and consistent findings have emerged. In healthy people, identifying facial emotions results in activation of a network that includes the limbic (amygdala and hippocampus), visual (fusiform), frontal (medial and inferior), and thalamic regions.[12-14] A growing literature in schizophrenia, applying block design fMRI, suggests diminished limbic activation for facial emotion processing tasks.[15-17] Few studies have examined cerebral activity in relation to symptom dimensions. Differences have been observed between patients with and without

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paranoia[15,18,19] and between those with and without blunted affect.[20]

Event-related fMRI permits further dissection of regional activation than that feasible with block design approaches. When tasks are presented in blocks of stimuli associated with specific instructions, their comparison to a baseline stimulus establishes activation for the overall top-down (executive) control effects in response to task demands. Event-related fMRI can measure signal change time locked to the induced bottom-up effects of appearance of specific stimuli within a task. This feature is especially useful for examining deficits associated with neuropsychiatric disorders because activation can be linked to the response, separating correct from incorrect processing. Correlating blocked effects with performance can be difficult to interpret, whereas activation concomitant with performance can pinpoint aberrant processing.

The purpose of the present study was to examine brain circuitry involved in the identification of facial emotions in schizophrenia. We applied a hybrid (blocked and event-related) design that enabled characterization of both task-related and stimulus-related activation. For the latter, the design provided separation of correct from incorrect identifications. The stimuli included happy, sad, anger, fear, and neutral expressions, which are universally recognized[21] and represent both social and threat-related emotions.[22,23] The hybrid design was set to answer 2 consecutive questions. The blocked analysis specifies regions activated by a task that required identification of a target emotion compared with a resting fixation on a stimulus with comparable features. The event-related analysis can focus on activated regions to examine hemodynamic changes, within these regions, that are time locked to the appearance of a face showing a specific emotion and how this differs between correct and incorrect responses. We hypothesized that top-down (blocked analysis) activation would occur in a network that includes limbic, frontal, and thalamic regions, with patients showing less robust activation. We further hypothesized that bottom-up (event-related) effects would show error-related differences with more pronounced abnormalities associated with flat affect. In schizophrenia, flat affect relates to emotion expression deficits and has been linked to impaired performance on emotion identification tasks.[4]

METHODS

PARTICIPANTS

The original sample included 20 patients and 20 healthy controls, who were consecutive right-handed volunteers at the Schizophrenia Research Center. However, 4 patients and 2 controls were excluded from further analysis because of excess motion (>4 mm), and 1 control participant was excluded for an incidental finding of abnormal structural MRI. The final sample included 16 patients with schizophrenia (12 men) and 17 healthy controls (12 men), who completed the study with high-quality data. The patients were approximately 5 years older on average (patients: mean ± SD, 30.1 ± 6.5 years; range, 21-41 years; controls: mean ± SD, 25.0 ± 3.9 years; range, 19-33 years; $t_{31}=2.73$; $P=.01$) and as expected had a lower educational level (patients: mean ± SD, 12.8 ± 2.3 years; range, 9-16 years; controls: 15.8 ± 2.2 years; range, 12-20 years; $t_{30}=3.72$; $P<.001$). However, they had comparable parental educational levels (patients: mean ± SD, 14.1 ± 3.6 years; range, 7-20 years; controls: mean ± SD, 16.3 ± 2.9 years; range, 9-20 years; $t=1.95$; $P=.06$). After complete description of the study, written informed consent was obtained.

Participants underwent standardized assessment procedures, including medical, neurologic, psychiatric, and neurocognitive evaluations and laboratory tests. The psychiatric evaluation for patients included clinical assessment with the Structured Clinical Interview for *DSM-IV*,[24] which was conducted by a trained clinical research coordinator; history obtained from family, health care professionals, and records; and scales for measuring symptoms administered by investigators trained to a criterion reliability of 0.90 (intraclass correlation). Patients had a *DSM-IV* diagnosis of schizophrenia established in a consensus conference based on all information available and had no history of other disorders or events that affected brain function, including no comorbid psychiatric diagnoses. The consensus conference includes a formal presentation of the research participants by research psychiatrists who conduct an intake clinical interview. The information is presented in a written summary that integrates all available data. In the consensus conference, members of the Clinical Core independently describe their diagnostic formulation of the case presented. These formulations are discussed and a consensus is reached and entered in the database. Mean ± SD age at onset of psychotic symptoms in the context of functional decline was 20.1 ± 3.8 years (range, 12-29 years), with an illness duration of 9.6 ± 7.1 years and 3.6 ± 4.1 (range, 0-15) hospitalizations. These clinically stable outpatients had mild symptoms at the time of the study. Global ratings on the Scale for Assessment of Negative Symptoms (SANS)[25] averaged 1.3 ± 0.9 (range, 0-3.0), and ratings on the Scale for the Assessment of Positive Symptoms (SAPS)[26] averaged 1.4 ± 0.6 (range, 0-2.3). At the time of imaging, 1 patient was untreated with antipsychotics and 15 were receiving stable doses: 2 received first-generation (chlorpromazine equivalents = 542 ± 292 per day),[27,28] 11 received second-generation (olanzapine equivalents = 18.2 ± 2.8 per day),[29] and 2 received both (chlorpromazine equivalents = 16.7 per day, olanzapine equivalents = 11.3 per day) medications. Controls underwent the same evaluation procedures.[30] They had no history of major psychiatric illness in first-degree relatives.

PROCEDURES

Imaging Tasks

The face emotion identification task included 4 conditions (separate time series), presented in a counterbalanced order, each with a specific target expression: happy, sad, anger, or fear. Stimuli were selected from a set validated in healthy people[31] and patients with schizophrenia.[29] The specific task conditions were further piloted to ensure comparable performance for target emotions in patients and controls, yet with sufficient number of errors to permit performance-based analysis of time series data. Each condition included four 90-second blocks of emotion identification, separated by 24 seconds of rest during which a scrambled face with a central cross-hair for fixation was displayed (**Figure 1**). Each block contained 8 target faces (eg, 8 fear), 12 foil faces (eg, 4 happy, 4 sad, 4 angry), and 10 neutral faces. Thus, a condition included a total of 120 faces: 32 target, 48 foil, and 40 neutral in a pseudorandom sequence. Faces appeared for 3 seconds, and participants endorsed "target" or "other" using the 2-button response pad.

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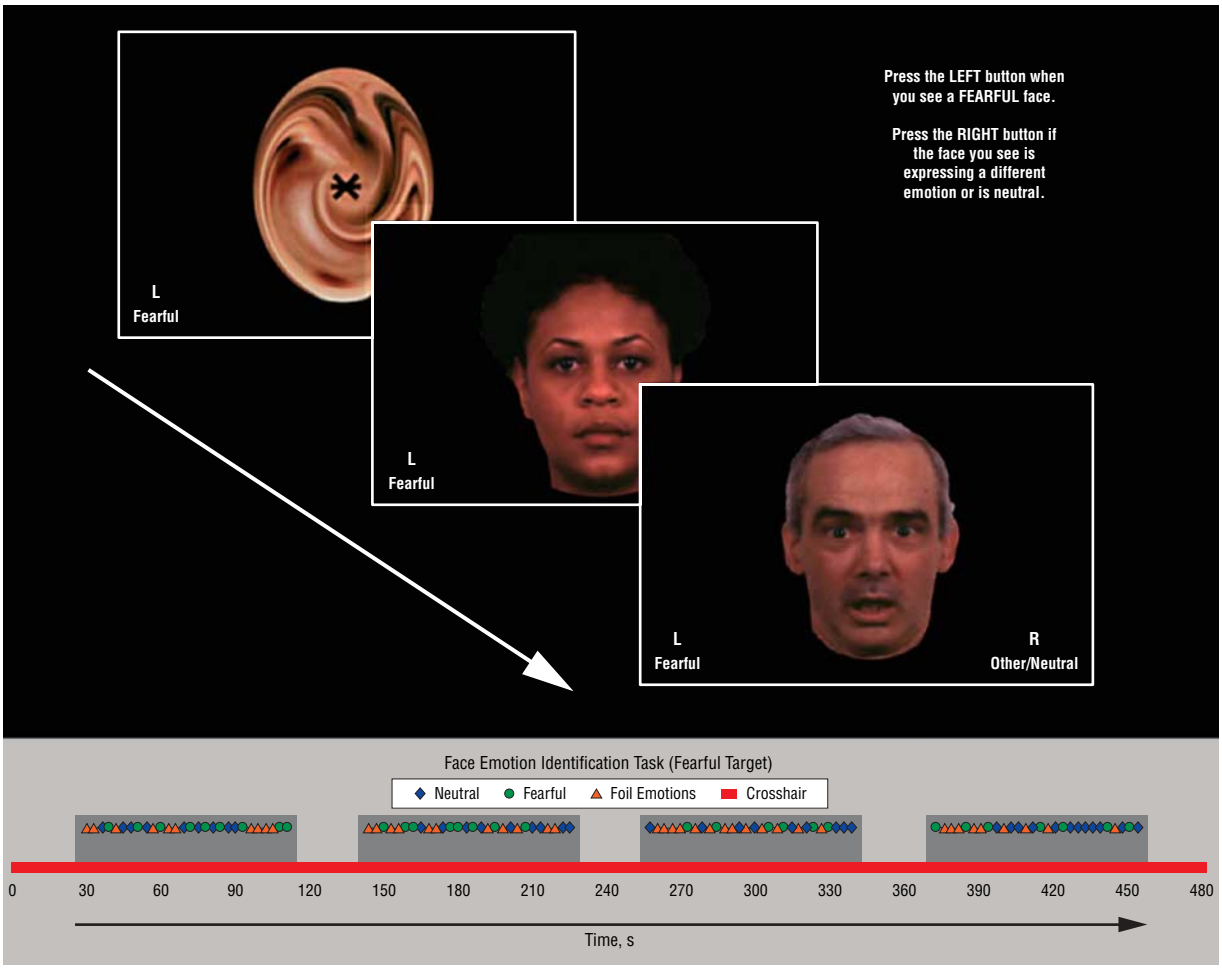

Figure 1. Face emotion identification task (fearful target).

Within a block, target expressions (eg, fear) and foil expressions (eg, happy, sad, or anger) were separated by a variable number of neutral faces (range, 0-5 faces, which equals 0-15 seconds), allowing for event-related modeling of the hemodynamic response with neutral faces as a within-block baseline. This interblock design also permitted modeling of events based on accurate target identification and errors. Abbreviated response instructions remained visible throughout the task. The same faces were cycled through the 4 conditions serving as targets or foils, depending on the condition, and they were equally distributed for sex and balanced for ethnicity (65% white, 23% African American, and 11% other). Each condition (time series) lasted 8 minutes, with a total task duration of approximately 32 minutes.

fMRI Procedures

Participants were administered a brief practice task before placement in the scanner. Earplugs were fitted to muffle noise, and head fixation was ensured through a foam-rubber device mounted on the head coil. Stimuli presentation was triggered by the scanner and synchronized with image acquisition using PowerLaboratory[32] (MacLaboratory Inc, Devon, Pennsylvania) on a Macintosh computer (Apple, Cupertino, California). Stimuli were rear-projected to the center of the visual field using a PowerLite 7300 video projector (Epson America Inc, Long Beach, California) and viewed through a head coil–mounted mirror. Participants were randomly assigned use of their right or left hand, and responses were recorded via a nonferromagnetic keypad (Current Design Inc, Philadelphia, Pennsylvania).

Image Acquisition

Data were acquired on a 4-T scanner (GE Signa Scanner; General Electric, Milwaukee, Wisconsin), using a quadrature transmit-and-receive head coil. Structural images consisted of a sagittal T1-weighted localizer, followed by a T1-weighted acquisition of the entire brain in the axial plane (24-cm field of view and 256×256 matrix, resulting in a voxel size of $0.9375 \times 0.9375 \times 4$ mm). This sequence was used for spatial normalization to a standard atlas[33] and for anatomic overlays of the functional data. Functional imaging was performed in the axial plane using a 16-slice, single-shot, gradient-echo, echo-planar sequence (repetition time/echo time = 1500/21 ms, field of view = 240 mm, matrix = 64×40, section thickness/gap = 5/0 mm). This sequence delivered a nominal voxel resolution of $3.75 \times 3.75 \times 5$ mm. The 5-mm section thickness was a compromise to permit optimal visualization of the amygdala with minimal sacrifice in brain coverage. Because of the size of the amygdala in the z direction (approximately 10 mm), we avoided using section gaps to increase coverage. Total sections per volume were also limited by a 1.5-second repetition time, which was selected to pro-

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vide 2 volume acquisitions per stimulus exposure (3 seconds per face). The sections were acquired from the superior cerebellum up through the frontal lobe. Inferiorly, this corresponded to a level just below the inferior aspect of the temporal lobes and superiorly to approximately the level of the hand-motor area in the primary motor cortex.

Because the gradient echo echoplanar images can be degraded in the presence of nonuniform magnetic fields, we paid special attention to the image quality in the anterior medial temporal lobes. An automated shimming was performed manually in a region of interest that contained the anterior medial temporal lobe.[34] After the shimming, pilot echoplanar images were obtained, which were visually inspected before fMRI acquisition to ensure good image quality in the amygdala region. The images were then corrected for residual geometric distortion[35] based on a magnetic field map acquired with a 1-minute reference scan.

STATISTICAL ANALYSIS

Performance Analysis

Differences in the percentage correct of all responses (true positive and true negative) and response time (in milliseconds) for correct responses were evaluated for each of the 4 target emotions. They were analyzed using separate repeated-measures diagnosis × emotion analyses of variance (ANOVAs), with 1 grouping and 1 repeated-measures factor. To satisfy the normality assumptions of ANOVA, the arcsine transformation was applied to percentages.

Image Analysis

The fMRI data were preprocessed and analyzed using FEAT (FMRI Expert Analysis Tool) version 5.1, part of Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's Software Library (www.fmrib.ox.ac.uk/fsl). Images were section time corrected with the Fourier-space time series phase shifting, motion corrected to the median image using trilinear interpolation with 6 *df*,[36] high pass filtered (120 seconds), spatially smoothed (8-mm full width at half maximum, isotropic), and scaled with mean-based intensity normalization. The median functional and anatomical volumes were coregistered then transformed into the standard anatomical space (T1 Montreal Neurological Institute template) with the trilinear interpolation, and the brain extraction tool was used to remove nonbrain areas.[37-39]

Subject-level time series statistical analysis was performed with Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's Improved Linear Model with local autocorrelation correction.[39] Each time series (ie, happy, sad, anger, fear) was regressed to a canonic hemodynamic response function modeling emotion discrimination blocks relative to crosshair. These data were submitted to group-level analyses. First, each participant's mean activation across the 4 target conditions and across all responses was calculated. To identify within-group effects, the averages (across 4 conditions) were entered into a separate single-group *t* test for patients and control participants. Differences between diagnostic groups were examined with 2-sample *t* tests, masked by the corrected and binarized single sample results (ie, controls > patients contrast masked by controls > baseline and patients > controls contrast masked by patients > baseline). To test for regions differentially activated by happy, sad, anger, or fear target conditions, the β weights for each target emotion were entered into a voxelwise repeated-measures ANOVA with 1 grouping (diagnosis) and 1 repeated-measures (target emotion) factor. All *z* (gaussianized T or F ratios) statistical images were corrected for spatial extent (AFNI AlphaSim; R. W. Cox, National Institutes of Health, Bethesda, Maryland) using a minimum *z* threshold of 2.33 or greater and a cluster $P<.05$ (for display, control > baseline is presented at $z \geq 4.20$ because of the large number of activated voxels). The cluster's peak *z* score coordinates were labeled using the Talairach Daemon database,[40] and region labels were then confirmed by manual examination of peak values and cluster centroid coordinates.

The event-related subject-level analysis modeled 5 performance-based regressors (correct target, incorrect target, correct foil, incorrect foil, and no response), with neutral faces serving as baseline. Mean scaled β coefficients (percentage of signal change) for correct and incorrect target identifications were extracted for offline analysis from regions identified in the block analysis using atlas-derived regions of interest (Wake Forest University pickatlas).[41] We also performed voxelwise analyses of the event-related data and examined group differences in activation for correct and incorrect responses to each target emotion.

Offline analysis of the percentage of signal change was performed using SAS statistical software (SAS Institute Inc, Cary, North Carolina). The activation data were entered into a group (schizophrenia, controls) × emotion (happy, sad, anger, fear) × region × correct vs incorrect repeated-measures multivariate ANOVA. Significant interactions were decomposed by univariate analyses. Spearman correlations were calculated between the percentage of signal change (across correct and incorrect trials) and the SANS[25] and SAPS[26] clinical rating subscales. The average ratings for each subscale were used for these correlations, rather than global ratings, because they provide smoother and more normally distributed scores.

RESULTS

PERFORMANCE

Performance data are summarized in **Table 1**. For the percentage correct, no main effect of diagnosis was found ($F_{1,31}=2.33$; $P=.14$). However, a main effect for emotion was found ($F_{3,93}=33.78$; $P<.001$). Both groups performed better for happy than the other expressions (post hoc least significant difference, $P<.05$). For response time, likewise no between-group differences were found ($F_{1,31}=0.26$; $P=.61$), but a main effect for emotion was found ($F_{3,93}=5.83$; $P=.001$), again with the happy faces being recognized faster than the others (post hoc least significant difference, $P<.05$). A similar pattern was observed when examining correctly identified target emotions (true-positive responses) with no main effect of diagnosis ($F_{1,31}=3.41$, $P=.07$) and a significant main effect for emotion ($F_{3,93}=15.60$, $P<.001$) also due to the happy condition (post hoc least significant difference, $P<.05$). There were no group × emotion interactions.

BLOCKED ANALYSIS

The blocked analysis showed significant activation for the emotion identification task in a distributed network of regions that included clusters in amygdala, hippocampus, thalamus, fusiform gyrus, and frontal and visual association cortex. The activation was more robust in controls than in patients. As seen in **Figure 2** and **Table 2**,

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Table 1. Performance During Emotion Identification in Patients With Schizophrenia and Healthy Controls

Performance Measure	Mean (SD) [Range]	
	Patients (n=16)	Controls (n=17)
Percentage of total correct		
Happy	90.66 (10.72) [45.00-97.50]	95.97 (5.21) [73.33-98.33]
Sad	77.90 (18.52) [25.83-86.66]	84.21 (18.41) [35.00-92.50]
Anger	79.87 (16.57) [23.33-90.00]	86.08 (10.54) [47.50-94.17]
Fear	76.90 (13.47) [41.67-86.67]	82.42 (12.11) [41.67-89.17]
Response time, total correct, ms		
Happy	931 (139) [700-1261]	890 (133) [631-1089]
Sad	1000 (147) [757-1303]	949 (181) [540-1289]
Anger	1024 (177) [638-1325]	1020 (152) [707-1201]
Fear	979 (167) [677-1286]	983 (202) [740-1371]
Target correct (maximum, 32)		
Happy	25.94 (5.42) [14-32]	28.12 (3.87) [20-32]
Sad	18.94 (8.13) [9-30]	21.82 (7.80) [10-30]
Anger	17.00 (6.56) [10-26]	18.12 (5.74) [11-27]
Fear	12.19 (6.44) [9-23]	18.94 (5.02) [9-25]

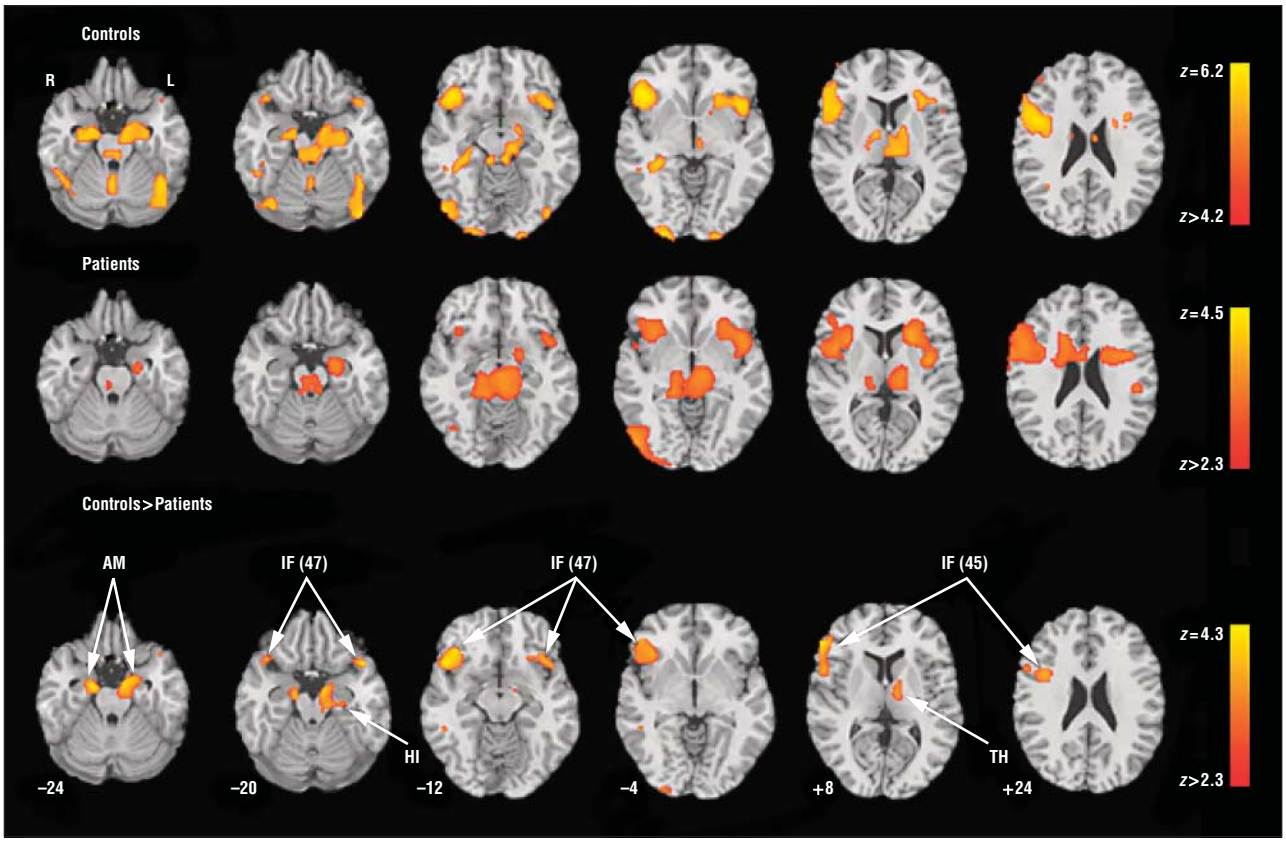

Figure 2. Regions activated for emotion identification task relative to baseline (block analysis) in controls (upper row), patients (middle row), and the controls–patients contrast (bottom row). No patients–controls contrast survived correction. Significance thresholds are based on spatial extent using a height of $z \geq 3.1$ and a cluster probability of $P \leq .05$. Images are displayed over a Talairach-normalized template in radiological convention (left hemisphere to viewer's right). The *z*-level coordinates are provided. AM indicates amygdala; IF (47), inferior frontal (Brodmann area 47); HI, hippocampus; IF (45), inferior frontal (Brodmann area 45); and TH, thalamus.

several regions showed significantly greater activation in controls, yet no region showed the reverse. No region showed differential activation among the target conditions when corrected for spatial extent. Inspection at a liberal threshold ($P < .05$, uncorrected) revealed that the anterior portion of the inferior frontal gyrus was less active in the happy condition. This effect seemed stronger in the control group, but no diagnosis × emotion interaction was observed at $P < .05$, uncorrected. Although the order of conditions (target emotion) was counterbalanced, we examined order effects in view of evidence for amygdala habituation.[42] The order effect was not statistically significant, and no order × diagnosis interactions were found.

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Table 2. Local Maxima, Coordinates, and Brodmann Areas of Blood Oxygenation Level–Dependent Functional Magnetic Resonance Imaging Signal Change Relative to Scrambled Face Baseline (Block Analysis) for Patients With Schizophrenia, Healthy Controls, and Group Contrasts

	Controls			Patients			Controls vs Patients		
Region (Brodmann Area) and Hemisphere	No. of Active Voxels	x, y, z[a]	Maximum *z* Score	No. of Active Voxels	x, y, z[a]	Maximum *z* Score	No. of Active Voxels	x, y, z[a]	Maximum *z* Score
Middle occipital gyrus (18)									
Right	389	38, –82, –18	5.27	64	26, –102, –2	3.53	60	28, –98, –4	2.64
Fusiform gyrus (37)									
Left	528	–46, –84, –20	5.67	. . .	. . .	. . .	. . .	. . .	. . .
Right	152	42, –56, –28	4.97	. . .	. . .	. . .	5	50, –44, –18	2.63
Thalamus									
Right	270	12, –8, 14	5.23	92	16, –18, 2	2.42	158	10, –4, 20	2.64
Amygdala									
Left	1994	–12, –10, –26	5.08	1440	–6, –20, –14	4.03	1265	–10, –8, –26	3.68
Right	285	20, –8, –26	5.34	230	24, –12, –28	3.59	249	18, –8, –24	3.74
Hippocampus									
Right	326	30, –36, –6	5.04	. . .	. . .	. . .	103	34, –28, –18	2.93
Inferior frontal (47)									
Left	997	–28, 20, 14	5.42	845	–26, 20, 12	4.17	392	–50, 16, –18	4.30
Right	3193	48, 28, –2	6.09	2695	36, 18, 0	3.81	2450	48, 20, –12	3.87
Middle frontal gyrus (9)									
Left	215	–40, 8, 30	5.18	41	–36, 4, 26	3.52	. . .	. . .	. . .
Right	68	48, 60, 4	4.86	9	50, 56, 10	2.57	. . .	. . .	. . .

[a] Coordinates from the Talairach stereotaxic atlas.[33]

EVENT-RELATED ANALYSIS

Contrast maps between patients and controls were generated, separating correct from incorrect responses to emotional relative to neutral faces and thresholded at an uncorrected significance level of $P \leq .001$ ($z \geq 3.1$). No significant voxels differentiating patients from controls were found in response to happy and sad faces, but significant differences in amygdala and other limbic regions emerged for anger and fear (**Figure 3** and **Table 3**). As can be seen in Figure 3 (top row), controls showed greater activation for correct responses to the appearance of angry faces in inferior frontal and orbitofrontal regions and had a maximum that fell just mesially to the amygdala proper in Brodmann area 34 (10, –1, –10; $z=3.69$) with a second peak at 12, –2, 18 ($z=3.66$). For fear (Figure 3, bottom row), controls showed greater activation in inferior frontal cortex for correct responses, but the most pronounced finding was of greater activation in patients associated with incorrect responses. This effect is especially notable in the amygdala bilaterally (Table 3). To examine the distribution of activated voxels in this region, we applied a more liberal threshold ($z=1.96$, $P=.01$, uncorrected; see insert in Figure 3). A visual comparison of 2 different group contrasts can be misleading, but the differential effects for anger (controls > patients) and fear (patients > controls) are in strikingly different limbic regions. As can be seen in the image, the medial activation associated with anger (controls > patients) abuts the more lateral activation associated with fear.

Analysis of the percentage of signal change (event-related model) extracted from the regions of interest that were identified in the blocked analysis showed that patients and controls had a nearly identical pattern and magnitude of activation time locked to the specific appearance of emotional compared with neutral faces. When performance was ignored, the diagnosis × region ANOVA on the percentage of signal change produced no main effects or interactions across emotions. Separately modeling the percentage of signal change for correct and incorrect responses, however, revealed a significant diagnosis × correct vs incorrect interactions with emotion and region. Specifically, the diagnosis × correct vs incorrect × emotion × region ANOVA showed significant effects for region ($F_{6,186}=9.31$, $P<.001$; emotion: $F_{3,93}=3.15$, $P=.03$; correct vs incorrect × region: $F_{6,186}=2.22$, $P=.04$; correct vs incorrect × emotion: $F_{3,93}=3.53$, $P=.02$; region × emotion: $F_{18,558}=1.70$, $P=.04$; and correct vs incorrect × region × emotion: $F_{18,558}=2.08$, $P=.006$). The interactions that involved diagnosis were diagnosis × correct vs incorrect × emotion ($F_{3,93}=4.28$, $P=.007$) and diagnosis × region × emotion ($F_{18,558}=2.09$, $P=.005$). As can be seen in **Figure 4**, both groups showed activation of the facial affect processing network that differed for correct compared with incorrect responses. Greater activation was generally associated with incorrect identification of happy faces and correct identification of sad, anger, and fear faces. The source of the interactions with diagnosis is that patients showed less activation for correct identification of the threat-related expressions of anger and fear (2 upper right panels in Figure 4) and greater activation for incorrectly identified fear stimuli (right column, middle panel of Figure 4). Indeed, the correct-minus-incorrect subtraction (bottom panels of Figure 4) showed that in controls greater

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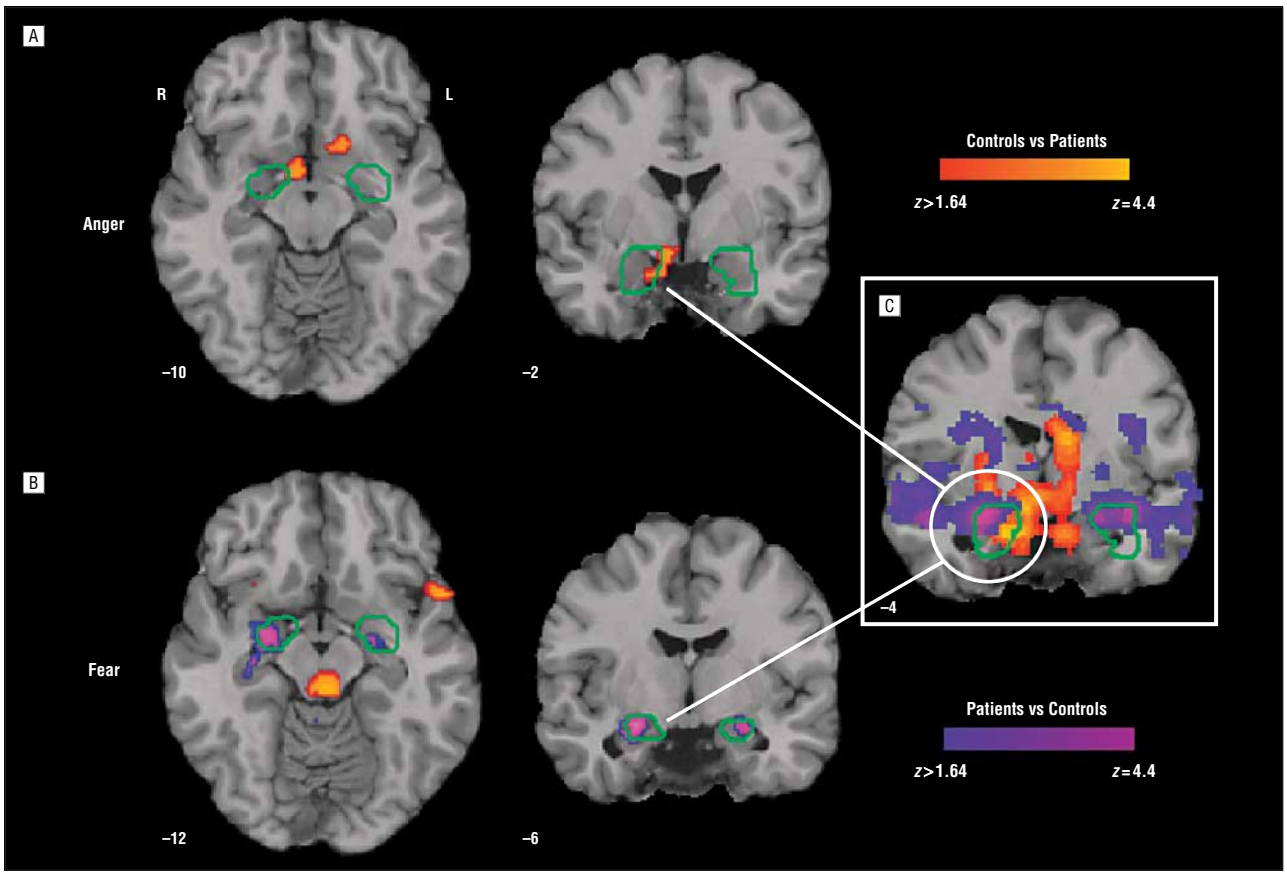

Figure 3. Activation maps showing peak amygdala response (see Table 3) for anger (A) and fear (B) conditions for the event-related analysis. Images are displayed over a Talairach-normalized template in radiological convention and thresholded at $z \geq 3.1$, uncorrected (>25 continuous voxels). Outline (green) shows extent of atlas-derived amygdala regions of interest (Wake Forest University pickatlas) used for percentage of signal change extraction. Insert (C) highlights patients' > controls' (blue) incorrect responses superimposed on controls' > patients' (red) correct responses at $z \geq 1.64$, uncorrected.

activation was associated with correct than with incorrect responses for anger and fear in most regions. By contrast, in patients the activation was greater for incorrect than for correct responses, especially for fear. This finding was confirmed by follow-up univariate analyses (available from the authors). The difference between patients and controls in the correct-minus-incorrect measure was significant for anger in fusiform gyrus and amygdala and for fear in all regions. Because the groups differed in age, the analyses were repeated covarying for age, as well as educational level and parental educational level, without diminishing the reported findings. Furthermore, an analysis of a subsample of 14 patients and 14 age- and parental educational level–matched controls did not change the results. In addition, because patients had more incorrect responses on average, we compared a subsample of 11 patients and 11 controls matched for performance on the fearful faces and determined that they had an identical pattern of activation (eFigure; available at http://www.archgenpsychiatry.com). Finally, medication type and dose did not relate to any of the dependent measures.

ASSOCIATION WITH CLINICAL MEASURES

The correlations between event-related changes and clinical severity ratings on the SANS and SAPS subscales were generally nil or low, except for very high correlations between severity of affective flattening or blunting subscale and activation of the thalamus, amygdala, and hippocampus in response to the appearance of fear expressions. This correlation was especially high for amygdala (r_{16}=0.937, P<.001) (**Figure 5**). Examination of the distribution of scores (Figure 5) indicated that the correlation was not caused by an outlier but reflected a smooth association across the range of available scores. We also repeated the correlational analysis on the global ratings of the subscales with similar results.

COMMENT

Patients with schizophrenia and healthy participants showed robust cerebral activation for a facial affect processing task in a network that includes limbic and thalamic components and visual association and frontal regions. As in earlier studies,[15-19] patients showed reduced activation in these regions compared with controls. Thus, emotion processing deficits in schizophrenia seem related to failure to recruit components of the neural system required for top-down facial affect processing tasks. This analysis, however, is not capable of differentiating brain activity related to different aspects of facial affect processing. Notably, amygdala activation was robust for

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all blocks, regardless of the target emotion, and no habituation effects were observed in either group. Although habituation effects to presentation of fearful stimuli have been reported,[42] these are diminished when the emotion is task relevant.[16,43]

Examination of the event-related responses, representing bottom-up effects of the appearance of emotional stimuli compared with neutral stimuli, provided further insight into neural substrates for affect processing deficits in schizophrenia. As indicated by the lack of a main effect of diagnosis, when performance is not considered, patients generally showed hemodynamic changes similar to controls to the appearance of faces across emotions. However, they diverged from controls in activation associated with correct compared with incorrect responses. Whereas in controls greater activation was related to correct identifications of anger and fear, in patients greater activation portended failure to identify the emotion. This divergence was specific to threat-related expressions, evident in fusiform gyrus and amygdala for anger and in nearly all components of the network for fear. Notably, the anger effects (controls > patients for correct responses) are more medial than the fear finding (patients > controls for incorrect responses). We believe this post hoc finding is intriguing but should be replicated prospectively.

The paradoxic association of greater network response to the appearance of an emotional face with failure to identify the emotion suggests that patients are operating within a maladaptive range, where increased activity results in deteriorated performance. We have reported with isotopic methods that both low and high anxiety, compared with medium levels, are associated with reduced cortical blood flow and performance.[44,45] Perhaps increased amygdala activation triggers reduced functioning of the cortical regions necessary for correct identification and labeling of facial expressions.[46] Compensatory activation could also explain behavioral response failure associated with increased hemodynamic response.

Correlation of regional activation with symptom severity measures revealed a specific association between higher magnitude of amygdala activation to the appearance of a fearful face and more severe affective flattening. This relationship is consistent with the abnormality in activation for correct compared with incorrect responding. Meta-analyses of fMRI experiments in healthy people,[13,14] as well as studies targeted to examine this issue,[47,48] support a fear-sensitive response of the amygdala. In schizophrenia both the amygdala and hippocampus show activation abnormalities in response to fearful faces.[18] Thus, in a blocked analysis patients had no amygdala activation habituation with repeated presentation of fearful faces.[49] Similarly, fear-related abnormalities were observed in both activation and performance, assessed after scanning.[18] It is unclear why flat affect is associated with increased amygdala response to fearful faces. Possibly it is an adaptation for faulty signaling from the amygdala.[50] These findings can be examined in light of an extensive literature on fear conditioning in rodents,[10,11] with paradigms that are applied in human fMRI studies.[51,52]

Table 3. Local Maxima, Coordinates, and Brodmann Areas of Blood Oxygenation Level–Dependent Functional Magnetic Resonance Imaging Signal Change for Fear and Anger Conditions for Correct Responses and Incorrect Responses in the Event-Related Performance-Based Model

Region (Brodmann Area) and Hemisphere	No. of Active Voxels	x, y, z[a]	Maximum *z* Score
Control vs Patient Correct Responses			
Fear			
Brainstem			
Left	259	0, −27, −5	4.39
Superior temporal gyrus (38)			
Left	91	−51, 13, −12	3.91
Inferior frontal gyrus (47)			
Right	92	36, 19, −18	3.71
Cingulate gyrus (23)			
Right	44	4, −26, 25	3.58
Lentiform nucleus			
Right	49	12, 6, 0	3.56
Left	44	−6, 2, −2	3.54
Anger			
Inferior frontal gyrus (44, 45)			
Right	99	46, 16, 10	3.76
Amygdala (34)			
Right	126	10, −1, −10	3.69
Middle frontal gyrus (10)			
Right	44	36, 58, 1	3.52
Subcallosal gyrus (25)			
Left	82	−10, 11, −11	3.44
Patient vs Control Incorrect Responses			
Fear			
Amygdala			
Right	242	28, −6, −11	4.10
Left	40	−24, −8, −13	3.68
Cuneus (18)			
Right	270	6, −89, 10	4.00
Middle temporal gyrus (39)			
Right	78	48, −67, 12	3.74
Precuneus (19)			
Left	66	−6, −85, 41	3.49

[a] Coordinates from the Talairach stereotaxic atlas.[29]

Our results suggest a different pattern of activation for happy and sad compared with anger and fear expressions. Perhaps, unlike the threat-related emotions of anger and fear, happy and sad expressions are more closely linked to the reward system. Abnormal activity in ventral striatum, an important limbic reward region, has been related to negative and positive symptom severity in schizophrenia.[53,54] A large body of evidence relates amygdala activity to negative emotions and aversive learning[10] and ventral striatal activity to positive emotions and reinforcement learning.[55] Both animal and human imaging studies[56-61] show dissociation of amygdala and ventral striatum responses to rewarding or aversive stimuli, which is consistent with functional antagonism between the 2 regions; however, there is also evidence of coactivation of amygdala and ventral striatum.[62-64] A balance of excitation and inhibition, both within[65] and between these structures, is likely necessary to achieve optimal response to rewarding, aversive, or threatening events. Comparing emotion identification to reward tasks in the same

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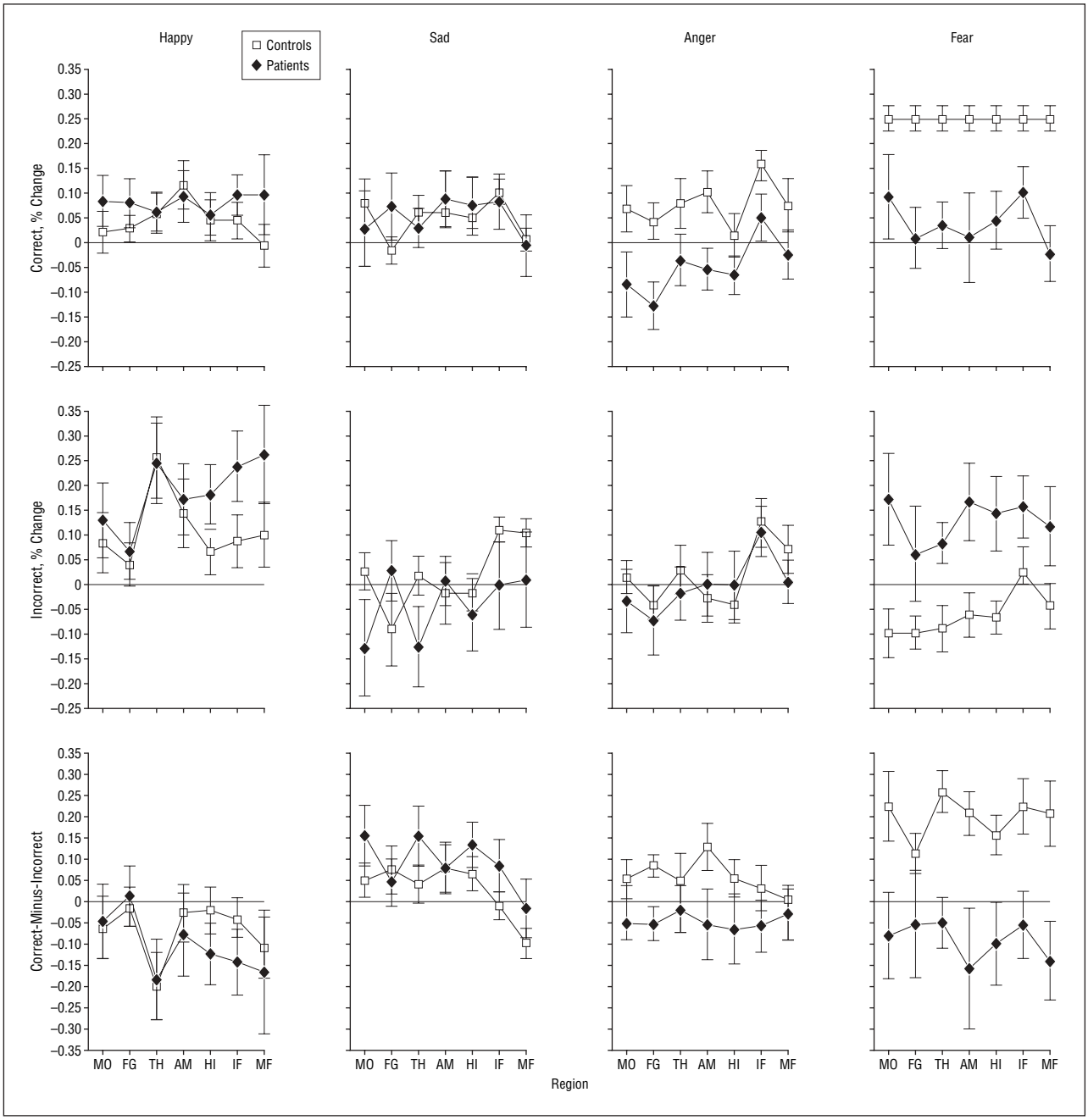

Figure 4. Event-related activation, in percent change units, relative to neutral faces, for correct (top row) and incorrect (middle row) identifications, and the correct-minus-incorrect subtraction (bottom row) for happy, sad, anger, and fear expressions in the activated regions: midoccipital (MO), fusiform gyrus (FG), thalamus (TH), amygdala (AM), hippocampus (HI), inferior frontal (IF), and midfrontal (MF).

patients and incorporating functional connectivity methods[66,67] may help elucidate both cooperative and reciprocal interactions between affective threat-related and reward-related systems.

The present study has several limitations. The sample size was powered to detect differences between patients and controls but not to examine subgroups to establish sex differences or effects of medications or chronicity. Therefore, our results should be considered cautiously with regard to whether they are similar in men and women and the extent to which they relate to medication or apply to samples with larger ranges of age or severity. Notably, our sample was predominantly male and controls were younger than patients. We have covaried for age and have analyzed a matched subsample of patients and controls, which did not affect the results. Another limitation of the study is that in an effort to cover the whole brain we failed to use smaller voxels in areas prone to susceptibility artifacts.[68] Although we used special shimming procedures for visualizing the amygdala, this approach may explain our failure to see effects in orbitofrontal regions. Furthermore, the hybrid design may have compromised our ability to obtain more robust estimates of event-related activation, as would have been feasible with sparse event-related designs and perhaps more limited brain coverage.[69] These improvements can be ex-

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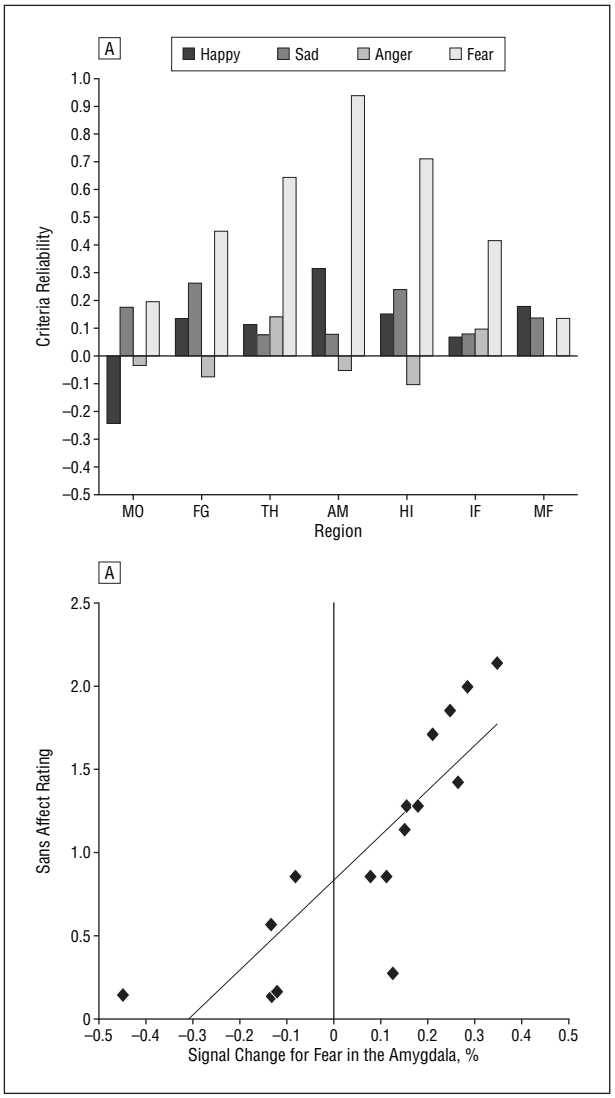

Figure 5. Association between brain activity and clinical measures. A, Correlations between event-related activation for the 4 emotional expressions in activated regions and severity of clinical ratings for flat affect. B, Scatterplot of the association between percentage of signal change for the appearance of fear expressions and severity of flat affect. Abbreviations are defined in the legend to Figure 4.

amined in future studies. Another limitation applies to the blocked analysis. Because participants only responded with button press to the faces and not to the scrambled-face baseline, task-related activation includes contributions of the motor component. However, for the event-related analysis our tight contrast included button pressing for all events.

Notwithstanding its limitations, the present study reports a novel observation related to emotion processing and flat affect in schizophrenia. The paradoxic finding in patients of greater bottom-up activation of the facial affect processing system associated with failure to recognize threat-related expressions is intriguing and merits further empirical evaluation. The high correlation between amygdala activation to fear expressions and severity of flat affect suggests that modulating this response could lead to better ways of addressing this heretofore treatment-resistant feature of schizophrenia.

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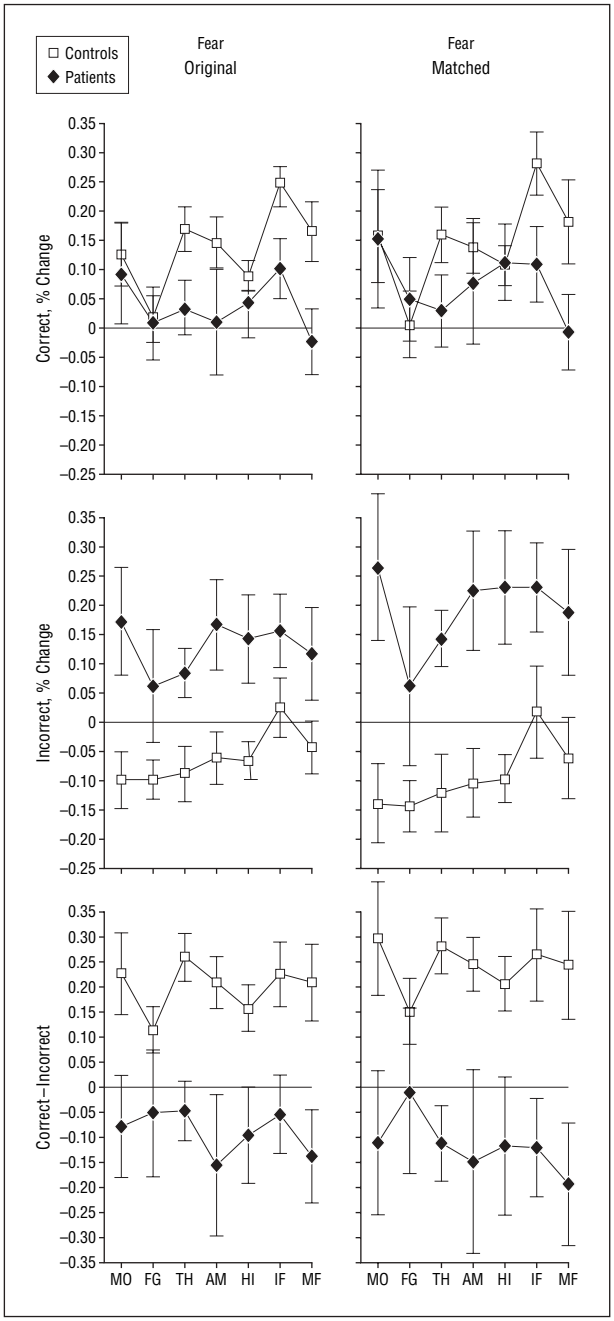

eFigure. This figure compares the effects shown in Figure 4 in the text (left column) with the same measures obtained on a subsample of 11 patients and 11 controls matched for performance on fearful faces (right column). It displays event-related activation, in percent change units, relative to neutral faces for correct (top row) and incorrect (middle row) identifications, and the correct–incorrect subtraction (bottom row) for fear expressions in the activated regions: midoccipital (MO), fusiform gyrus (FG), thalamus (TH), amygdala (AM), hippocampus (HI), inferior frontal (IF), and midfrontal (MF).

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