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Diminished Neural Sensitivity to Irregular Facial Expression in First-Episode Schizophrenia

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Abstract: *Introduction:* Blunted, inappropriate affective-social behavior is a hallmark of early schizophrenia, possibly corresponding to reduced ability to recognize and express emotions. It is yet unknown if this affective deficiency relates to disturbed neural sensitivity to facial expressions or to overall face processing. In a previous imaging study, healthy subjects showed less suppression of the fusiform gyrus (FG) to repeated presentation of the same transfigured-bizarre face relative to regular face. We assumed that the FG in schizophrenia will show reduced repetition related sensitivity to transfigured-bizarre faces, while having overall normal response to faces. *Methods*: Ten first-episode patients with schizophrenia and 10 controls rated the bizarreness of upright and inverted faces. In an fMRI study, another group of 17 first-episode patients with schizophrenia and 12 controls viewed regular and transfigured-bizarre faces in blocks. Each block contained regular- or transfigured-bizarre faces of either different or same individual, presented in an upright or inverted orientation. *Results:* Patients in comparison with controls rated irregular faces as less bizarre. The FG, in patients and controls exhibited similar response to inverted faces, suggesting normal face processing. In contrast, the FG only in patients, showed similar suppression to repeated transfigured-bizarre and regular faces. Finally, the FG in patients compared with controls showed reduced functional connectivity with the amygdala and prefrontal cortex. *Conclusion:* Patients with schizophrenia already at first-episode, showed reduced behavioral and neural sensitivity to bizarre facial expressions. Possibly, this deficiency is related to disturbed modulations of emotion-related face processing in the FG by the amygdala and prefrontal cortex. *Hum Brain Mapp 30:2606–2616, 2009.* **© 2009 Wiley-Liss, Inc.**

Key words: fMRI; repetition-suppression; fusiform-gyrus; amygdala; prefrontal cortex; modulation

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INTRODUCTION

Patients with schizophrenia often manifest deficient emotional behavior, expressed as blunted or inappropriate affective response in a social context [Flaum and Schultz, 1996]. One possible link between social and emotional behavior could be related to sensitivity to adequacy of facial expressions. Patients with schizophrenia indeed suffer from a markedly reduced ability to recognize and express face-related emotions [Addington and Addington, 1998; Gessler et al., 1989; Mandal et al., 1998]. It remains unclear whether this abnormality is related to deficient processing of faces per se or of their emotional expressions. Sorting out these aspects of face processing is especially difficult since they tend to interact [Calder et al., 2000]. This was recently demonstrated by a study showing that healthy controls had a greater accuracy in emotional detection for upright than inverted orientation of faces [Fallshore and Bartholow, 2003]. Intriguingly, perception of facial expression in schizophrenia was shown to be less affected by face inversion, suggesting that patients may use different strategies to decode emotional information from faces [Chambon et al., 2006].

Neural representations of facial processing have been extensively investigated by modern brain imaging techniques. The fusiform gyrus (FG) was verified as one of the major areas for face processing in the human healthy brain, showing selective response to faces compared with other objects [Kanwisher et al., 1997]. It was also shown that the FG is modulated by inverted orientation [Yovel and Kanwisher, 2004] and negative emotional content [Bleich-Cohen et al., 2006] of faces.

One way to study the sensitivity of a region for a stimulus' parameter is by looking if it modifies the amount of activation suppression to repeated presentation of the stimulus (i.e., repetition-suppression effect). This approach has been widely implemented in studying high-order visual processing including features of faces [Grill-Spector et al., 1999, 2006]. To study whether facial expressions modulate the repetition-suppression effect one needs to keep all other face-related features unchanged. In a previous fMRI study in our lab with healthy subjects, we separated between these parameters by applying the "Thatcher illusion," where face content is transfigured from regular to bizarre while keeping its local features largely unchanged [Thompson, 1980]. This previous fMRI study showed that "repetition-suppression" effect was diminished when facial expression were transfigured and rated as bizarre and unpleasant. Furthermore, greater inter-regional correlation between amygdala and FG to transfigured-bizarre faces, supported enhanced local cooperative computation of a "far-from-template" facial expression [Hendler et al., 2003; Rotshtein et al., 2001]. It can therefore be presumed that the degree of reduced selectivity of the repetition-suppression effect in the FG marks its sensitivity to facial content. Activation selectivity of the FG to emotional content could be mostly related to its modulation by other brain regions such as the amygdala. Indeed the FG has extensive reciprocal connections with the amygdala [Amaral et al., 2003] and the prefrontal cortex (BA 10,11) [PFC; Rolls, 1999a,b], both implicated in emotion processing of faces [Hasselmo et al., 1989; Krolak-Salmon et al., 2004].

In terms of schizophrenia there is disagreement on the effectiveness of face-related neural processing in the FG. Several studies showed a reduction in the overall response of the FG to faces in schizophrenia compared with healthy controls [Gur et al., 2002; Johnston et al., 2005; Yoo et al., 2005]. These findings are further supported by anatomical evidence of reduced volume of the FG in patients with schizophrenia [Ha et al., 2004; Lee et al., 2002; McDonald et al., 2000; Onitsuka et al., 2003, 2004, 2005; Pantelis et al., 2003]. Others argued that after controlling for individual anatomical differences, task difficulty and variability in the hemodynamic response, FG responses to faces in schizophrenia do not differ from healthy controls [Yoon et al., 2006]. Moreover, there is no agreement whether schizophrenia alters selective responses of the FG to the emotional content of faces [Phillips et al., 1999].

The overall goal of this study was to sort out whether patients with first episode schizophrenia suffer from abnormal neural processing of faces per se or of their emotional content. More specifically, behavior wise, we aimed to test the sensitivity to facial bizarreness in patients with schizophrenia relative to healthy controls. To manipulate facial expressions while keeping local facial features unchanged we applied the Thatcher's illusion procedure [see Rotshtein et al., 2001]. To test brain-related abnormalities in schizophrenia, we applied fMRI on another group of patients. The sensitivity of the FG to irregularities in facial expressions was tested by selectivity of repetition-suppression effect to regular and transfigured-bizarre facial expressions. We predicted that patients with schizophrenia compared with healthy controls will show diminished behavioral sensitivity to ET faces. Accordingly, it was also expected that patients will show reduced sensitivity of the FG to repeated presentation of bizarre faces along-side with overall normal response to face inversion.

MATERIALS AND METHODS

Experiment 1: Behavioral Sensitivity to Bizarre Facial Expression

Subjects

Ten right-handed patients with schizophrenia (age = 22–33 yrs; 7 men), first-episode of psychosis, hospitalized <1 month at the Beer Yaakov Mental Health Center were enrolled. They were either nonmedicated or medicated for <1 month with antipsychotic drugs with a rating on the Clinical General Impression (CGI) scale of 4–5. Psychiatrists verified patients' schizophrenia diagnoses according to DSM-IV criteria. None had prior history of neurological

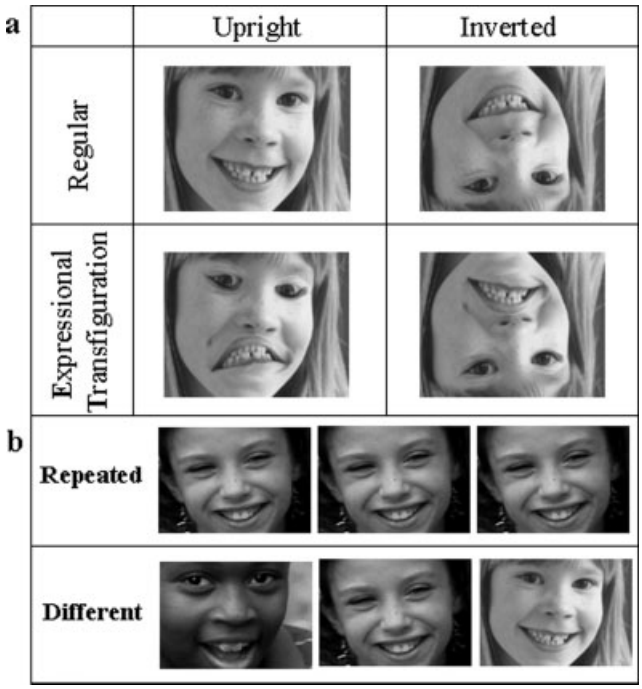

Figure 1.
Stimulus types and experimental design. (a) Example of face types: regular and ET expressions, and upright and inverted orientations (b) Repetition manipulation was done in blocks: each face type was presented in blocks of repeated or different presentations.

and substance abuse disorders based on physical and neurological examination, routine laboratory investigation and medical records. Ten right-handed matched controls participated (age = 24–31 yrs; 5 men) as a control group and were interviewed by a psychiatrist to exclude major neurological and psychiatric disorder. Before study entry, all participants provided written informed consent that was approved by the Beer Yaakov Mental Health Center Institutional Review Board.

Stimuli and task

The original visual stimuli consisted of 40 achromatic close-up photographs of faces presented in front view with a red fixation point added in the center of the image. The expressional transfiguration (ET) was obtained by 180° rotation of the eyes and the mouth of the regular face (Fig. 1a). Each face type was presented in upright and inverted orientations. Participants were requested to rate the bizarreness of each face on a scale of 1–5 (1 = "most bizarre," 5 = "least bizarre"). Stimuli were presented randomly for 0.9 s followed by a blank screen until the subjects responded. Presentation software (Neurobehavioral Systems, Inc., 2003) was used to present stimulus and record subjects' responses and the STATISTICA (version 5.0) software was used to analyze the data.

Results and discussion

Three-way analysis of variance (ANOVA) (group × orientation × expression) for repeated measures was preformed with orientation condition (upright/inverted) and expression (regular/ET) as factors within group and diagnosis (schizophrenia/healthy) as a between-group factor. We found that ET faces were judged as more bizarre than regular faces [main effect of expression, $F(1,19) = 87.56$; $P < 0.00001$, Fig. 2], and that this effect was mostly pronounced in the upright orientation [Interaction of orientation and expression ($F(1, 19) = 37.705$, $p = .00001$)]. This replicates numerous previous studies that tested for the effect of bizarreness on face perception [Rotshtein et al., 2001; Thompson, 1980].

The patients, but not the controls, rated all face types as less bizarre [main effect of group, $F(1,19) = 10.76$; $P < 0.005$) and this effect was more pronounced for the ET faces [two-way interaction of group by expression, $F(1,19)$

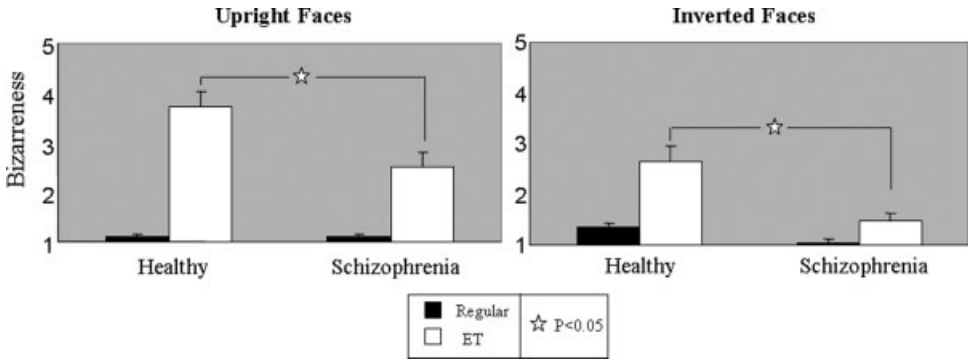

Figure 2.
Behavioral results of bizarreness ratings in patients with schizophrenia and healthy controls for regular and ET expressions in upright (a) and inverted (b) orientations. Error bars represent standard error of the mean (SEM).

TABLE I. Demographic and clinical data of schizophrenia patients

No	Age (year)	Gender	PANSS positive	PANSS negative	PANSS general	PANSS total	CGI-S	Length of hospitalization (days)	Medications
1	32	F	18	29	31	78	4	2	No
2	25	M	20	14	37	71	5	3	No
3	23	M	23	18	36	81	4	3	No
4	27	F	25	18	38	81	5	3	Risperidone (14 days)
5	35	M	17	15	23	55	3	5	No
6	24	M	30	20	41	91	5	7	No
7	27	F	24	22	28	74	5	9	Risperidone (7 days)
8	36	F	22	11	32	65	4	9	Clothiapine (7 days)
9	29	F	31	27	42	100	5	12	Risperidone (2 days)
10	30	M	21	17	30	68	4	14	Risperidone (11 days)
11	34	F	13	23	34	70	4	16	Clopixol (14 days)
12	24	M	26	16	34	76	4	17	Zuclopenthixol (2 weeks)
13	21	M	30	14	29	73	4	25	Zuclopenthixol (3 weeks)
14	21	F	12	19	48	79	4	28	Perphenazine (7 days)
15	21	M	28	21	35	84	5	28	Quetiapine (2 weeks)
16	34	F	25	17	34	76	5	35	Olanzapine (28 days)
17	28	M	32	21	33	86	5	56	Risperidone (28 days)

PANSS, Positive and Negative Symptom Scale; CGI, Clinical Global Impression.

= 11.39; $P < 0.005$]. Post-hoc analysis revealed that ET faces in both upright and inverted orientation were judged as less bizarre by the patients in comparison with the healthy controls (Tukey HSD post hoc $P < 0.0005$). This result concurs with the hypothesis that schizophrenia attenuates the ability to properly evaluate the meaning of irregularities within perceptual information. Thus, ET faces were perceived more normal-like by patients than by healthy controls.

Experiment 2: Neural Sensitivity to Bizarre Facial Expression

Subjects

Additional group of patients with schizophrenia and controls participated in the fMRI session. The study population consisted of 19 right-handed patients with schizophrenia (age = 21–35 yrs; 11 men) in their first episode of psychosis, all hospitalized for the first time at the Beer Yaakov Mental Health Center. The clinical evaluation procedure was similar to that of the behavioral study. Because of extensive head movements (head movement > 1.5 mm), two patients were excluded from the final analysis. Patients were either nonmedicated or medicated for <1 month (Table I). We obtained a measure of each schizophrenia patient's symptoms based on the Positive and Negative Syndrome Scale (PANSS) [Kay et al., 1987] and the CGI-S [Guy, 1976] (single rater RDS). Twelve age- and gender-matched right-handed healthy volunteers (age = 25–54 years; 7 men) were recruited as controls. All healthy subjects were interviewed by a senior psychiatrist to exclude any major neurological and psychiatric disorder. Before study entry, all subjects provided written informed consent that was approved by the Beer Yaakov Mental Health Center Institutional and the Tel Aviv Sourasky Medical Center review boards.

Visual stimuli

The baseline visual stimuli consisted of the same stimuli described in experiment 1 (Fig. 1a). The regular and ET faces, turned upside down, created the conditions of the inverted-regular and the inverted ET faces. Four of the faces, used in the repeated presentation conditions (see below), had an additional version in which their overall contrast level was reduced by 15% because of task requirements (see below). This was not expected to affect activation in high-order visual areas [Avidan et al., 2002].

fMRI experimental procedure

Visual stimuli were presented in a block design fashion. Epochs consisted of either different-faces (Diff) or repeated-face (Rep) conditions. In the Rep condition, the same face was presented 15 times, whereas in the Diff condition, 15 different faces from the same type were presented (Fig. 1b). The epochs were separated by 6–9 s in which subjects viewed a fixation point on a gray background. Each condition was presented two to four times within each scan session, in a design that balanced for the order of conditions. Stimuli presentation rate was 1 Hz (0.9 s a face interposed with 0.1 s blank). A 100 ms blank of mean luminance interposed between consecutive images to match the interimage transients in all blocks. The stimuli sequences were generated on PC and projected via an LCD projector (Epson MP 7200) onto a translucent tangent screen located on the head coil in front of the subject's forehead. Subjects viewed the screen through a tilted mirror fixed to the head coil. To equally engage the observer's

attention across ET and regular face conditions, subjects were asked to fixate on the red point and to perform a covert one-back-matching task through the whole run. They were instructed to indicate whether or not two successive faces were identical. In the Rep conditions, the difference was related to the contrast of the stimuli, whereas in the Diff conditions, the difference was related to identity of faces. In each epoch, three to four (of 15) stimuli created these differences. In the Rep condition, one image differed in its overall contrast (15%)—we encourage the reader to identify it, so as to appreciate the task difficulty involved.

MRI set-up

Imaging was performed on GE 1.5T Signa Horizon LX 8.25 echo speed scanner (Milawaukee, W1) with resonant gradient echoplanar imaging system. All images were acquired using a standard quadrature head coil. The scanning session included anatomical and functional imaging. The anatomical images were high resolution sagital localizer acquired in the beginning of each scanning session. Seventeen contiguous axial T1-weighted slices of 4-mm thickness, 1-mm gap were prescribed, based on the sagital localizer, covering the whole brain except the most dorsal and ventral tips. In addition, a 3D spoiled gradient echo (SPGR) sequence, with high resolution, was acquired for each subject, to allow volume statistical analyses of signal changes during the experiment. Functional T2*-weighted images were acquired (at the same locations as the spin-echo T1-weighted anatomical images), in runs of 2856–2890 images (168–170 images per slice). fMRI acquisition parameters were as follows: TR/TE/flip angle = 3000/55/90°; with FOV 24 × 24 cm^2 matrix size 80 × 80.

Data analysis

fMRI data were processed using BrainVoyager4.4 and QX1.8 software package [Goebel et al., 1998a,b] (http://www.brainvoyager.com). Comparison of the raw functional data with the two-dimensional (2D) structural scan enabled an estimate of the extent of signal dropout attributable to a susceptibility artifact for each subject. Functional images were incorporated into the three-dimensional (3D) data sets through trilinear interpolation. The complete data set was transformed into Talairach space [Talairach and Tournoux, 1988]. Preprocessing of functional scans included head movement assessment (scans with head movement > 1.5 mm were rejected), high-frequency temporal filtering, and removal of low-frequency linear trends. Three-dimensional statistical parametric maps were calculated separately for each subject using a general linear model (GLM) [Friston et al., 1995] in which all stimuli conditions were positive predictors, with a lag of 3–6 s (to account for the hemodynamic response delay). In addition, the first six images of each functional scan were rejected to allow for T2* equilibration effects.

Regions of interest analysis in the fusiform gyrus

Based on our a-priori hypothesis, we focused our analysis on the fusiform gyrus. The definition of the regions of interest (ROI) was done based on anatomical constraints of previously reported functional foci in the fusiform gyrus [i.e., Talaraich coordinates: left fusiform gyrus: -36 ± 3, -53 ± 3, -16 ± 4; right fusiform gyrus: 36 ± 3, -53 ± 3, -16 ± 4; see Rotshtein et al., 2001]. We then extracted from each individual an averaged time course obtained across voxels that showed larger responses to faces than to fixation within these anatomical regions ($P < 0.005$ uncorrected). Significance tests were performed on the average percent signal change for each condition per group. Four-way ANOVAs for repeated measures were preformed with orientation condition (upright/inverted), expression (regular/ET), and repetition (repeated/different) as factors within group and diagnosis (schizophrenia/healthy) as a between-group factor. For each face type, repetition-suppression ratio was calculated by dividing the repeated condition by its corresponding different condition. A ratio of 1 indicated no suppression. Finally, we analyzed the activation in the fusiform gyrus based on the symptoms exhibited by the patients, as obtained from the clinical assessment. In this analysis, we divided the subjects into two groups in accordance to the median of several parameters of the clinical symptoms, such as positive, negative, general and total symptoms, clinical global impression (CGI), medication, age, length of hospitalization, and gender (see Table I). We then tested the correlation between these clinical measurements and the responses we observed in each patient's fusiform gyrus.

Whole brain analysis

Using random effect models, we compared brain responses of healthy controls and patients with schizophrenia to test for any significant differences that were outside our a-priori ROIs. We compared responses with face versus fixation, ET versus regular faces, upright versus inverted faces, and responses to different versus repeated condition at threshold of $P < 0.005$ with random effect.

Correlation map analysis

We applied interregional correlation analysis using time courses obtained from the left and right fusiform gyri [Friston et al., 1993, 1995]. The "seed region" was anatomically defined based on our a-priori ROI in the fusiform gyrus in each cortical hemisphere. Time courses were obtained individually from a 20-voxel cluster in the fusiform area that showed the most significant repetition-suppression effect for ET faces (note that although the overall suppression effect for ET faces was small in the healthy group, it yet existed at a sub-cluster of voxels within the fusiform gyrus). The average time course was used as a predictor in GLM to compute a voxel-by-voxel fit. A second-level random-effect based group analysis with FDR of 0.0001 was applied to determine

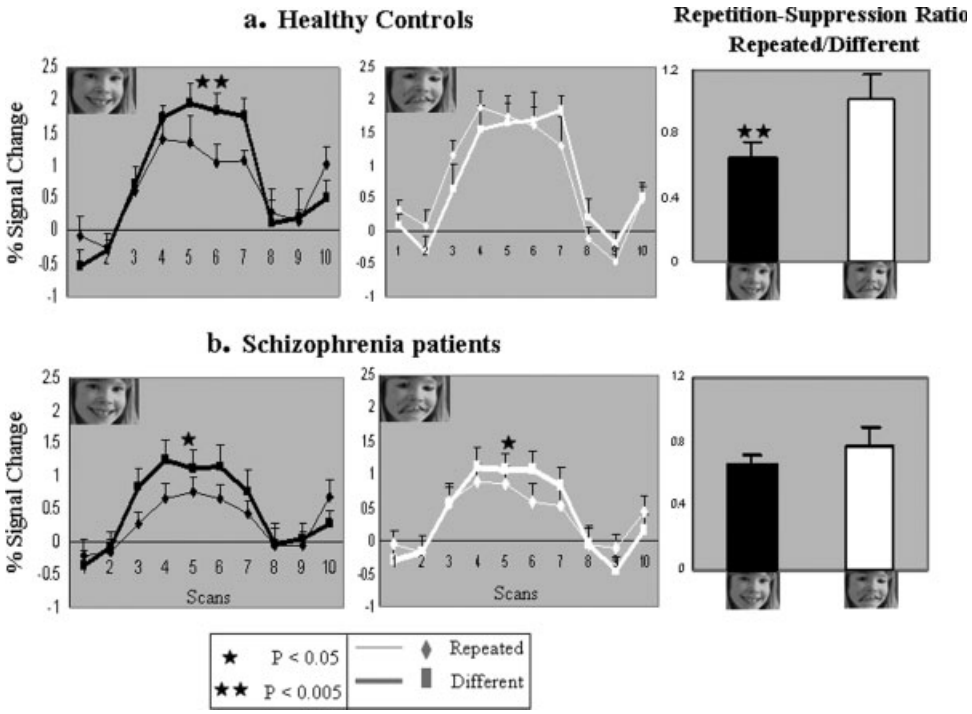

Figure 3.

Repetition-suppression effect in the fusiform gyrus: Overlay time-courses and calculated ratio (right column) of averaged percent signal change for different (bold line) and repeated (thin line) presentations of faces with regular and ET expressions, presented for the healthy controls (a) and patients with schizophrenia (b) groups. Error bars represent standard error of the mean (SEM).

the brain areas that showed significant functional connectivity with the fusiform gyrus across subjects. This second level analysis revealed significant activation in the amygdala and PFC of the healthy controls in comparison with the patients. Thus, we quantified the between-group differences in the amygdala and PFC (BA 10, 11) by counting the number of activated voxels in each subject in these two brain regions and performed a Mann-Whitney U test on the number of voxels in the bilateral amygdala and PFC between the two groups.

Results of Experiment 2

ROI analysis in the fusiform gyrus

A four-way ANOVA (group × orientation × repetition × expression) was preformed with group (schizophrenia/healthy) as a between factor and orientation (upright/inverted), repetition (repeated/different), and expression (regular/ET) as within factors. Both groups demonstrated more activation for ET than for regular faces [main effect

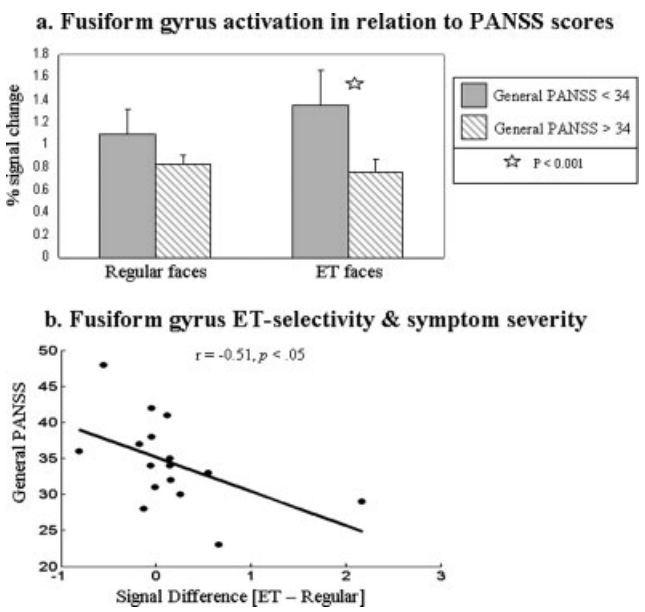

Figure 4.

Selective response of the FG to ET faces in relation to symptom severity measures by the PANSS. (a) Averaged percent signal changes in response to faces with regular and ET expressions for schizophrenia subgroups categorized by the general PNASS scale (>34 = gray, <34 = stripes). (b) Correlation between score on the general PNASS scale and the FG selective activation for ET relative to regular upright faces. The value of 1 means no selectivity.

TABLE II. Interaction between ET faces and repeated condition for controls

Region of interest	Left	Peak P	Right	Peak P
Fusiform gyrus			39, −50, −12	0.0028
Lateral occipital	−42, −65, −8	0.0192	49, −68, −6	0.0058
Middle temporal gyrus	−58, 1, −13	0.0011		
Precentral gyrus (BA 6)			51, −2, 31	0.0098
Middle frontal gyrus (BA 9/10)	−31, 41, 23	0.0075		
Lentiform nucleus, putamen			24, 9, 4	0.0070
Amygdala	−21, −7, −13	0.0013	22, −7, −17	0.0012

for expression, $F(1,27) = 9.554$; $P < 0.005$], more activation for upright than inverted faces [main effect for orientation, $F(1,27) = 10.388$; $P < 0.005$], and more activation for the different than repeated faces [main effect of repetition, $F(1,27) = 24.704$; $P < 0.0001$]. A three-way interaction [group × repetition × expression, $F(1,27) = 4.475$; $P < 0.05$] revealed that the groups differed significantly on effect of face content on repetition-suppression. Figure 3 displays this interaction effect via averaged time courses for repeated and different presentations (thin and bold lines respectively), per group [healthy (Fig. 3a) and schizophrenia (Fig. 3b)], and face type (regular and ET faces, the first and second columns, respectively). Post-hoc analysis revealed that there was a significant suppression effect for the ET faces only for the patients (Tukey LSD post hoc $P < 0.05$). To further demonstrate this interaction between face type and repetition, we calculated an averaged repetition-suppression ratio (see Methods section) for each group (Fig. 3a,b right column).

It's important to note that we conducted the same analysis without the older subject (age = 54) in the healthy group and still received the same significant effects and interactions. Therefore we did not exclude him. To explore the effect of symptoms on the fusiform activation we divided the patients into two subgroups; below and above the median (e.g. 34). This division based on scoring of the general PNASS scale revealed significant interaction of group by face type for fusiform activation for all face presentation [group × expression, $F(1,14) = 5.35$; $P < 0.05$]. There was difference in the FG activation between the groups that was greater for ET faces than for regular faces (Tukey HSD post hoc $P < .001$; Fig. 4a). Similarly the PNASS general scale scoring was negatively correlated with the difference in fusiform activation between ET and regular faces ($r = -0.51$, $P < 0.05$, Fig. 4b).

Whole brain analysis

We performed a whole brain analysis to test for any significant group differences that were outside our a-priori ROIs. The contrast of ET versus regular faces for the repeated condition revealed a different set of regions for each group. Healthy controls but not patients with schizophrenia had greater activation for ET than regular faces in the fusiform gyrus, lateral occipital cortex, middle temporal gyrus, precentral gyrus (BA 6), middle frontal gyrus (BA 9/10), lentiform nucleus, putamen, and amygdala (Table II). Figure 5 shows an overlay of activation maps obtained for each group for all face conditions versus fixation (group GLM, random effect, FDR $P < 0.01$). This overlay map reveals that although the healthy and patients with schizophrenia activated the visual areas with considerable overlap (purple color), the amygdala (white circle) was more active by the healthy controls (red color) than the schizophrenia group (blue color).

Whole brain voxel-based correlation with the fusiform time-course revealed considerable difference in the spatial extent of coactivations between the two groups. Overlay maps of the correlation maps obtained from each group shows that although both groups equally correlated in posterior regions with the fusiform gyrus, the patients with schizophrenia showed reduced correlation of the fusiform gyrus with the amygdala and PFC (see Fig. 6). Table III presents the regions that were coactivated with the fusi-

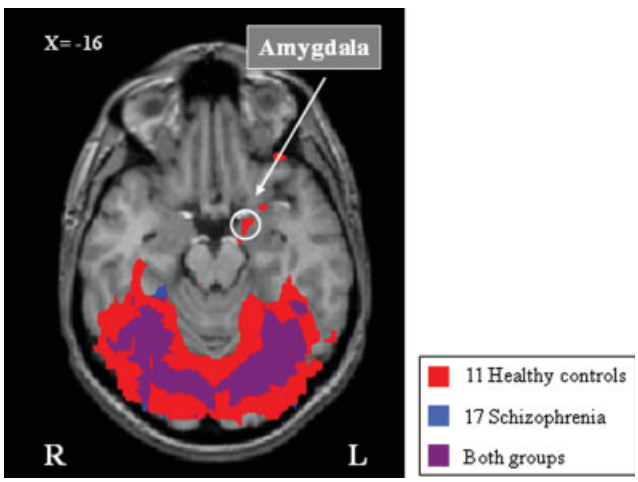

Figure 5.
Whole brain activation for all faces versus blank (FDR of 0.01, random effect for each group), shown as an overlay-map of 11 healthy controls (red), 17 patients with schizophrenia (blue), and both (purple). White circle marks the amygdala nucleus obtained only for the healthy group.

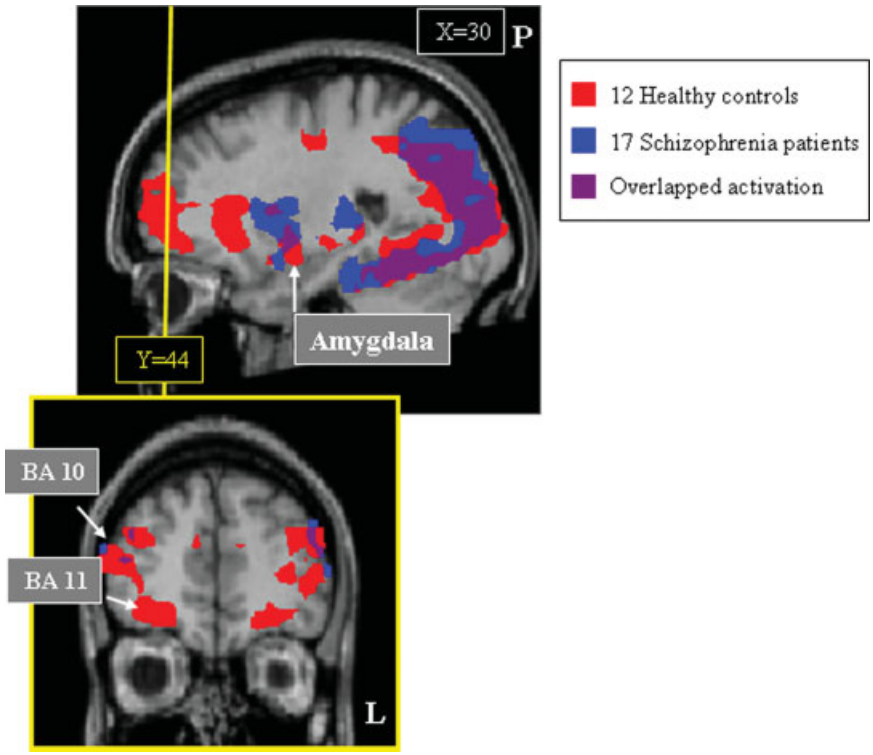

Figure 6.
Functional connectivity maps revealed by an averaged time-courses from right and left FG for upright ET faces in different versus repeated presentations (random effect, FDR of 0.0001). Overlay maps of functional connectivity are shown in sagital and coronal views for 12 healthy controls (red), 17 patients with schizophrenia (blue), and both (purple) groups. The arrows point to the PFC (BA 10, 11) and the amygdala where correlated activation with the FG was found for healthy controls but not for patients with schizophrenia.

form gyrus. Healthy controls but not the patients with schizophrenia demonstrated correlated activation in limbic areas, ventral prefrontal regions and the STS. We quantified the between-group differences in the amygdala and PFC (BA 11) by counting the number of correlated voxels. This analysis revealed significant decrease in the number of correlated voxels in patients with schizophrenia compared with healthy controls in bilateral PFC (BA 11) and bilateral amygdala. The *P* values for these comparisons calculated by Mann-Whitney U test are summarized in Table IV. It is worth noting that there was no significant correlation between symptom severities scales (PANSS

TABLE III. Functional connectivity with activation in the fusiform gyrus

ROI	Left	AvgPValue	*t*-score	Right	AvgPValue	*t*-score
A. Healthy controls						
PFC (BA 6)	−35, −9, 42	$0.1 \times 10^{-0.8}$	6.21	47, −4, 41	$0.1 \times 10^{-0.8}$	6.22
PFC (BA 8)	−45, 8, 34	$0.1 \times 10^{-0.8}$	6.79	43, 8, 34	$0.1 \times 10^{-0.8}$	6.43
PFC (BA 9/46)	−41, 30, 33	$0.6 \times 10^{-0.5}$	4.94	39, 34, 35	$0.6 \times 10^{-0.5}$	4.76
PFC (BA 10)	−18, 47, −6	$0.7 \times 10^{-0.5}$	4.72	21, 47, −6	$0.7 \times 10^{-0.5}$	4.89
PFC (BA 11)	−18, 48, −8	$0.2 \times 10^{-0.8}$	5.04	23, 47, −8	$0.8 \times 10^{-0.5}$	4.63
Intraparietal sulcus	−24, −59, 56	$0.2 \times 10^{-0.8}$	6.83	32, −58, 55	$0.1 \times 10^{-0.8}$	6.82
STS	−55, −37, 17	$0.7 \times 10^{-0.5}$	4.68	50, −42, 19	$0.6 \times 10^{-0.5}$	4.89
Amygdala	−15, −6, −14	$0.1 \times 10^{-0.8}$	7.12	25, −4, −12	$0.1 \times 10^{-0.8}$	6.63
Insula	−31, 23, 9	$0.1 \times 10^{-0.8}$	7.52	33, 21, 9	$0.1 \times 10^{-0.8}$	7.03
Thalamus	−9, −20, 3	$0.1 \times 10^{-0.8}$	6.48	5, −19, 4	$0.1 \times 10^{-0.8}$	6.81
Head of Caudate	−10, 16, 10	$0.1 \times 10^{-0.8}$	6.80	13, 17, 10	$0.1 \times 10^{-0.8}$	6.55
Lentiform				21, 8, 7	$0.1 \times 10^{-0.8}$	6.91
B. Schizophrenia patients						
PFC (BA 6)	−35, −11, 32	$0.1 \times 10^{-0.8}$	7.03	47, 3, 41	$0.1 \times 10^{-0.8}$	7.03
PFC (BA 8)	−37, 4, 34	$0.1 \times 10^{-0.8}$	6.12	44, 4, 34	$0.1 \times 10^{-0.7}$	6.23
PFC (BA 9/46)	−35, 33, 33	$0.1 \times 10^{-0.8}$	6.22	41, 34, 33	$0.1 \times 10^{-0.7}$	6.13
Intraparietal sulcus	−25, −59, 50	$0.1 \times 10^{-0.8}$	6.58	33, −66, 51	$0.1 \times 10^{-0.8}$	6.36
Insula	−31, 19, 9	$0.1 \times 10^{-0.8}$	6.57	34, 20, 9	$0.1 \times 10^{-0.8}$	6.42
Thalamus	−9, −18, 3	$0.1 \times 10^{-0.8}$	6.26	9, −19, 3	$0.1 \times 10^{-0.8}$	6.62
Lentiform	−23, 4, 7	$0.1 \times 10^{-0.8}$	6.38			

PFC, prefrontal cortex; STS, superior temporal sulcus.

TABLE IV. Significance of the between-group differences in the number of correlated voxels

Brain region	Left amygdala	Right amygdala	Left BA 11	Right BA 11
P value	0.063	0.011	0.00065	0.000056

positive, negative, and general scores) and numbers of correlated voxels in the PFC and amygdala.

DISCUSSION

The behavioral findings demonstrate that patients with schizophrenia already in their first episode suffer from reduced ability to detect bizarreness in faces. This seems to correspond to diminished neural sensitivity in the FG to repeated presentation of irregular facial expressions (e.g. ET). Unlike in healthy controls, the FG in patients with schizophrenia presented the same magnitude of suppression to both the repeated regular faces and bizarre ET faces. This abnormality correlated with the individual symptom severity according to general PANSS. Interestingly, the overall effect of repetition and inverted orientation of faces in the FG was similar in controls and patients with schizophrenia, suggesting normal face processing. Functional connectivity analysis supported the notion that disturbed interaction between the FG, amygdale, and the PFC (BA 10, 11) in patients with schizophrenia might contribute to the decreased neural sensitivity to bizarreness in faces.

In terms of the magnitude of visual activation it is worth noting that compared with healthy controls, patients with schizophrenia had less overall visual activation in the FG (see Fig. 3). This could be related to general effects of arousal possibly because of drug effect. To preclude drug treatment effect on the magnitude of activation in the visual cortex, we compared between patients with and without medication and found no difference. Interestingly, Miller et al. [1997] demonstrated that patients treated with antipsychotic drugs had significantly higher regional cerebral blood flow in the left FG compared with the 3 weeks off-medication condition. Indeed most of our patients received antipsychotic drug treatment for <4 weeks, a relatively short time for these drugs to be efficacious.

Reduced Face-Related Content Sensitivity in the Fusiform Gyrus

The content-related diminished effect of repetition-suppression in the FG of our healthy controls corresponds to our previous finding with the similar paradigm [Rotshtein et al., 2001]. The attenuation of this expressional modulation in patients with schizophrenia might contribute to low behavioral sensitivity to value bizarreness in facial expression.

The repetition-suppression effect in sensory brain regions is believed to reflect enhanced selectivity to a stimulus, possibly by reducing the recruitment of neurons upon its repeated presentation [Grill-Spector et al., 1999]. When considering the FG and its selectivity to faces, one can think of the repetition-suppression effect in terms of neural sensitivity to irregularities in the selective stimulus of this area (i.e., face). Accordingly, it is claimed that in our study patients with schizophrenia showed reduced sensitivity of the FG to irregular shape in the faces resulting in bizarre expressions. Since the bizarreness of ET faces was shown to correlate with unpleasantness [Rotshtein et al., 2001], it is impossible to sort out whether this content effect is related to irregularity and inadequacy (i.e., bizarreness) or negative valence of the ET faces. Support for the later comes from prior neuroimaging studies that demonstrated an emotional deficit in face processing by presenting less FG activation in response to faces in chronic schizophrenia patients than in healthy controls. For example, Taylor et al. [2002] showed that chronic schizophrenia patients in comparison with healthy controls had significantly less selective activation in the FG for negative relative to neutral content in pictures. Similarly, Fakra et al. [2008] presented decreased activation in the FG in chronic schizophrenia patients during a matching task of emotional faces in comparison with controls.

Does abnormal emotional processing in faces mark deficient social cognition in schizophrenia? Rating ET faces as relatively not-bizarre can be interpreted as a poor mechanism for assigning adequate social value for stimuli in the environment. This in turn might lead to inappropriate social behavior, a hallmark sign of acute schizophrenia. Intriguingly, the abnormality in the FG activation was unrelated to the severity of positive or negative symptoms as measured by the PNASS. Rather it was related to the score of general PNASS reflecting a decline in everyday functions such as interpersonal interaction and social behavior. Accordingly, our data indicate that the reduced sensitivity of the FG to ET faces was mainly contributed by the group of patients with the highest score on the general scale of the PANSS (see Fig. 4).

Reduced Face-Related Coactivation With the Fusiform Gyrus

Studies in primates have shown extensive reciprocal connections between the FG and the amygdala [Amaral et al., 2003], which is implicated in emotion processing of faces [Hasselmo et al., 1989; Krolak-Salmon et al., 2004; Morris et al., 1996, 1998]. In our study, we found both reduced overall activity of the amygdala (see Fig. 5) and weaker functional connectivity of the amygdala with the FG (see Fig. 6) in the patients compared with healthy controls. Our finding of increased left amygdala activation to all face contrast in the healthy controls is in agreement with the leading findings in the literature regarding lateralization of the amygdala [Baas et al., 2004; Fitzgerald et al., 2006]. Previous imaging studies showed reduced activation in the amygdala in patients with schizophrenia for sad mood induction [Schneider et al., 1998] and during a discriminative emotional valance task of faces [Gur et al.,

2002]. Here, we demonstrate that the amygdala is overall hypoactive to faces even when the task is irrelevant to emotion, pointing to a more general role of the amygdala in assigning value to a face through its social content. This idea is supported by recent finding from fMRI study in monkeys showing that the amygdala nuclei are sensitive to social content in faces [Hoffman et al., 2007]. The current finding of diminished connectivity between the amygdala and FG in schizophrenia, uniquely point to a possible role of the amygdale in contributing to the reduced sensitivity of the FG to face-related content in patients.

Another region that clearly showed reduced functional connectivity with the FG in schizophrenia is the PFC (BA 10,11). This area is known to receive dense inputs from several processing levels in the visual cortex [Rolls, 1999a,b]. The relevance of these areas to emotional processing is suggested by the evidence of dense reciprocal connections between the PFC and the amygdala. Moreover, damage to the ventral PFC is known to cause major deficits in social and emotional behavior in humans. For example, it was shown that patients with lesions in the PFC are impaired in face and voice expression identification [Hornak et al., 2003]. Structurally disorganized prefrontal but not parietal fiber tracking in first episode schizophrenia further supports the possibility that the reduced functional connectivity in the current study is related to deficient modulation of the FG by the prefrontal cortex [Mendelsohn et al., 2006]. Further studies are needed to sort this causal relation.

Our finding regarding the relation between PFC and the FG echo with the idea that disturbed long-distance connections between frontal and posterior brain regions encompasses the core neuropathology in schizophrenia [Andreasen et al., 1999; Friston, 1998]. This concept recently gained backing from neuroimaging studies. For example, although both the anterior cingulate and the cerebellum showed a task-specific relationship with the medial superior frontal gyrus in healthy volunteers, this relationship appears to be disrupted in schizophrenia [Honey et al., 2005]. Furthermore, there was decreased functional connectivity in schizophrenia during rest compared with healthy controls, and such an abnormality was widely distributed throughout the entire brain [Liang et al., 2006].

In conclusion, decreased behavioral and neural sensitivity to bizarre facial expression may underlie disturbed social behavior already in early stages of schizophrenia. Our results strongly suggest that this abnormal processing of facial expressions is not because of problems in face processing per se in the FG. Rather inter-regional correlation analysis points to decreased face-related coactivation between the FG the amygdala and the PFC.

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