



Altered brain responses to specific negative emotions in schizophrenia

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ABSTRACT

Deficits in emotion processing are a core feature of schizophrenia, but their neurobiological bases are poorly understood. Previous research, mainly focused on emotional face processing and emotion recognition deficits, has shown controverted results. Furthermore, the use of faces has been questioned for not entailing an appropriate stimulus to study emotional processing. This highlights the importance of investigating emotional processing abnormalities using evocative stimuli. For the first time, we have studied the brain responses to scenic stimuli in patients with schizophrenia. We selected scenes from the IAPS that elicit fear, disgust, happiness, and sadness. Twenty-six patients with schizophrenia and thirty age-, sex- and premorbid IQ-matched healthy controls were included. Behavioral task results show that patients tended to misclassify disgust and sadness as fear. Brain responses in patients were different from controls in images eliciting disgust and fear. In response to disgust images, patients hyperactivated the right temporal cortex, which was not activated by the controls. With fear images, hyperactivation was observed in brain regions involved in fear processing, including midline regions from the medial frontal cortex to the anterior cingulate cortex, the superior frontal gyrus, inferior and superior temporal cortex, and visual areas. These results suggest that schizophrenia is characterized by hyper-responsivity to stimuli evoking high-arousal, negative emotions, and a bias towards fear in emotion recognition.

1. Introduction

Deficits in emotion processing are a main feature of the symptom spectrum in patients suffering from schizophrenia. This impaired emotional functioning includes deficits in emotional expression, perception, and recognition (Kring and Elis, 2013; Trémeau, 2006). Moreover, schizophrenia patients report less positive and more negative emotional states and less pleasant events in their daily life compared to

controls (Oorschot et al., 2012). However, the neurobiological basis of emotional impairments in schizophrenia is still poorly understood. Most neuroimaging research about emotional processing has focused on face processing, based on the hypothesis that altered emotional facial expression recognition is linked to social cognition deficits in schizophrenia. These studies have linked emotional processing deficits in psychosis to abnormal activity of prefrontal regions, amygdala, hippocampus and visual areas (Dyck et al., 2014; Dzafic et al., 2018; Mier

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et al., 2014; Sabharwal et al., 2017; Spilka et al., 2015; Spilka and Goghari, 2017). Recent works, considering that the emotional processing impairment in schizophrenia especially affected negative stimuli, have focused on studying the processing of emotional faces expressing fear, anger or disgust, finding altered activity in structures like the amygdala or the prefrontal cortex (Hall et al., 2008; Lindner et al., 2016; Liu et al., 2011; Rauch et al., 2010; Szabó et al., 2017; Williams et al., 2004).

Nevertheless, research about emotional processing employing faces has revealed some limitations. First, studies show inconclusive results: while some works have reported hyperactivation of the above-mentioned brain areas (prefrontal regions, amygdala, hippocampus and visual areas) (Dyck et al., 2014; Dzafic et al., 2018; Sabharwal et al., 2017) others have shown hypoactivation in those same areas (Dzafic et al., 2018; Gur et al., 2002; Mier et al., 2014; Sabharwal et al., 2017; Spilka et al., 2015; Spilka and Goghari, 2017). Even in studies focused exclusively on negative emotional faces, some works report hyperactivation in amygdala and prefrontal cortex (Lindner et al., 2016; Liu et al., 2011; Rauch et al., 2010; Williams et al., 2004), others find a hypoactivation pattern in the same areas (Hall et al., 2008; Szabó et al., 2017; Williams et al., 2007), or even an absence of differences between patients and controls (Holt et al., 2005). Second, behavioral research about emotional face processing has also shown inconclusive results. While some studies found that patients with schizophrenia presented more difficulties in recognizing negative facial expressions than positive ones (Bediou et al., 2005; Edwards et al., 2001; Kohler et al., 2003; van't Wout et al., 2007), later research found no evidence of impaired recognition for negative emotions such as fear, disgust and sadness, when testing intellectually preserved patients (Pankow et al., 2013; Pomarol-Clotet et al., 2010).

A third limitation is that the use of faces has been questioned for not entailing an appropriate stimulus to study emotional processing. Neuropsychological models of face processing propose a brain system that deals specifically with facial information, including information related to emotional and identity recognition (Ellis and Young, 1988; Calder & Young, 2005). Therefore, it is possible that responses seen in studies using facial stimuli (both in neuroimaging and behavioral research) might partly reflect processing of other sources of facial information. For example, neuroimaging studies support the existence of separate systems for the analysis of faces: one for invariant features such as identity, related to brain responses in the superior temporal gyrus, and another for variant features such as emotions related to the lateral fusiform gyrus (Haxby et al., 2000). Results from emotional face processing studies might reflect alterations in these systems or their interaction, instead of altered emotion processing *per se*. Moreover, emotional facial expressions do not necessarily elicit the subjective experience of emotions (Davidson and Irwin, 1999).

Moreover, face processing might impose additional cognitive demands and does not capture responses to other types of emotional stimuli. As an alternative, the task of simply viewing emotionally salient pictures could minimize the cognitive demands of face processing and would be suitable for examining automatic emotional responses (Takahashi et al., 2004). However, only a small number of studies have employed non-facial stimuli to investigate emotional processing in schizophrenia. Hägele et al. (2016) studied brain responses to positive, negative and neutral scenic images from the International Affective Picture System (IAPS; Lang et al., 1997) in different diagnostic groups including schizophrenia and a healthy control group. They found a significant response to positive images in the prefrontal cortex, middle temporal gyrus and precuneus, and a significant response to negative images in the amygdala and middle temporal gyrus across diagnostic groups, with no differences between them. In schizophrenia patients, Pankow et al. (2013) studied the amygdala's response to negative and positive scenic stimuli from the IAPS, finding a hyperactivation to negative images and a hypoactivation in response to positive images in comparison to healthy controls. Finally, Takahashi et al. (2004) studied

brain responses to negative scenic images compared to neutral scenic images, finding reduced activation in the right amygdala, bilateral hippocampal regions, prefrontal cortex, basal ganglia, thalamus and visual areas in schizophrenia.

However, these previous studies using scenic stimuli only differentiated between positive and negative valence, but not between more specific emotional categories. Brain responses to scenic stimuli selected to evoke specific emotions (i.e. happiness, sadness, disgust and fear) have been studied before in a sample of healthy controls (Radua et al., 2014). Results showed brain responses in regions broadly similar to those observed in studies using facial emotion tasks, like limbic and extra-striate visual areas, as well as additional responses not reported using facial stimuli. For example, previous research had shown a response in the amygdala to happy faces (Fusar-Poli et al., 2009), which was not observed in response to happy scenes. Additionally, while activity in the amygdala-hippocampus, insula and fusiform gyrus was observed in response to scenic disgusting images, these areas showed a deactivation pattern in response to happiness and sadness, differing from previous studies using faces. These differences in brain response to specific emotional types of stimuli possibly reveal different systems involved in the processing of faces and scenic images and highlight the potential of this approach to complement findings from studies using faces and offer a better understanding of the neurobiology of emotion processing abnormalities. Given that there are no studies in schizophrenia differentiating between emotional categories beyond positive or negative valence using scenic stimuli, the objective of this study was to examine, for the first time, brain altered responses to basic emotions (i.e. fear, disgust, happiness and sadness) in schizophrenia patients in comparison to healthy controls using ecological emotional scenes. We hypothesized that brain regions activated by the task in patients and controls would be similar to those involved in the processing of emotional scenes previously found in healthy adults to the same emotional categories (Radua et al. 2014). Most of previous research using faces have found impaired brain response to negative emotions in schizophrenia (i.e. disgust, fear or anger), with an abnormal response in brain areas normally involved in response to these negative emotions (i.e. Lindner et al., 2016; Liu et al., 2011; Rauch et al., 2010; Szabó et al., 2017). However, studies using scenes have not differentiated between those emotional categories, finding inconclusive results when accounting for positive or negative emotions (Hägele et al., 2016; Pankow et al., 2013; Takahashi et al., 2004). According to those results we could further hypothesize that most differences between schizophrenia patients and healthy controls will be related to the processing of specific negative emotions, such as fear.

2. Methods

2.1. Participants

Fifty-seven adults meeting DSM-IV-TR criteria for schizophrenia or schizoaffective disorder recruited from Benito Menni CASM Hospital and Mare de Déu de la Mercè Hospital in Barcelona participated in the study. They all underwent diagnostic evaluation by trained raters using the Spanish version of the Structured Clinical Interview for DSM Disorders (SCID). Psychotic symptoms were also scored using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1989). Patients were excluded if they a) were younger than 18 or older than 65 years, b) were left-handed, c) had a history of brain trauma or neurological disease, or d) had shown alcohol/substance abuse within 12 months prior to participation. They also had to have a premorbid IQ in the normal range, as estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP; Del Ser et al., 1997; Gomar et al., 2011). All patients were taking medication.

Healthy controls (n = 30) were drawn from a larger cohort to be matched to the patients in age, sex, and premorbid IQ, to avoid biases in brain and cognitive function due to these variables. After discarding

nonvalid participants due to excessive head movement or poor behavioural performance in the post-scanning test (they wrongly classified more than 50% of the images as previously presented or new), a sample of 30 healthy controls (a sample size similar to that for patients) was selected, prior to analysis and blind to results, considering sex distribution and the mean and standard deviation for age and premorbid IQ (TAP) for the patients sample. The control sample met the same exclusion criteria as the patient sample. They were also excluded if they reported a history of mental illness or treatment with psychotropic medication, and/or had a first-degree relative with a psychiatric illness. The SCID was also used to exclude any current psychiatric disorder.

Final sample characteristics are reported in Table 1. All participants gave written informed consent prior to participation. All the study procedures were approved by the Research Ethics Committee FIDMAG Sisters Hospitaliers (Comité de Ética de la Investigación de FIDMAG Hermanas Hospitalarias) and complied with its ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Emotional pictures task

The task during the scanning session consisted of 80 photographs depicting ecological scenes selected to elicit emotional responses (20 of disgust, 20 of fear, 20 of happiness, and 20 of sadness) and there were also 40 photographs depicting ecological scenes, showing non-emotional material (neutral). All images were selected from the IAPS database (see Appendix). Participants were instructed to simply look at the photographs. The presentation was divided in 24 blocks, each composed of 5 photographs of the same emotion type or neutral. In order to avoid the emotional effect from the content of previous blocks to be added to the present images, each block was followed by a 'washout' period in which 3 simple symbols such as ampersands were presented. Each photograph or symbol was presented for 4 s, so that each block lasted for 20 s, plus 12 s of washout (see Fig. 1). Emotional blocks were presented in a counterbalanced order in order to avoid sequence effects. For example, photographs of happiness were presented once after photographs of sadness, once after photographs of fear, once after photographs of disgust and once after neutral photographs.

After the scanning session, participants were presented with the same 120 photographs, plus 34 new photographs (19 emotional and 15 non-emotional or neutral). They were instructed to state whether they

Table 1
Demographic and clinical sample characteristics.

	Patients (n = 26)	Controls (n = 30)	p
Sex (M/F)	24/2	24/6	0.177
Age	38.46 (9.45) range 18–59	38.13 (11.02) range 20–63	0.906
IQ/pre-morbid IQ (TAP)	99.08 (10.30) range 77–114	102.63 (5.89) range 87–112	0.135
Illness duration	12.2 (8.44) range 3–28		
PANSS Total score	73.79 (19.21) range 39–122		
PANSS Positive	15.88 (6.42) range 7–31		
PANSS Negative	22.46 (5.86) range 10–32		
PANSS General	35.46 (9.69) range 20–61		
Treatment (mg/day in CPZ eq.)			
Typical Antipsychotics	227.47 (188.01) range 13.83–533.2		
Atypical Antipsychotics	479.29 (291.83) range 26.67–1100		

Note. Measures are means (SD). Group differences were tested with a Chi-squared test for sex and unpaired two-sample *t*-test for age and IQ.

had previously seen the photograph in the scanner or not, to evaluate the intensity and valence of the emotion evoked using The Self-Assessment Manikin (SAM; Bradley & Lang, 1994) by dragging a bar using the computer mouse, and to specify the type of emotion shown in the photograph. Participants' answers were re-coded into: a) percentage of photographs correctly classified as previously presented or new; b) mean emotional valence-signed intensity of the photographs presented during the scanning session (from highly negative to highly positive); c) mean absolute emotional intensity of the photographs presented during the scanning session (from neutral to high); and d) percentage of online photographs correctly classified according to the emotional type (same classification as in Radua et al. (2014) was used). If participants did not correctly classify (as previously presented or not) more than 50% photographs, they were considered not to have attended the task during the scanning session and excluded from the rest of the study, this criteria of wrongly classify more than 50% of the images was the same used by Radua et al. (2014) in healthy adults.

2.3. Image acquisition

All subjects underwent fMRI scanning using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona (Spain). In each individual scanning session 394 volumes were acquired. A gradient-echo echo-planar (EPI) sequence depicting the blood-oxygenation-level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 40 ms, flip angle 70°, section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution 3x3 mm. The first ten volumes were discarded to avoid T1 saturation effects, and visual inspection of the raw images led to the detection of technical artifacts in the datasets. High-resolution structural T1 MRI data were obtained for anatomical reference and inspection with the following parameters: number of axial slices 180; slice thickness 1 mm, slice gap 0 mm, matrix size 512 × 512; voxel resolution 0.5 × 0.5 × 1 mm³; echo time (TE) 4 ms, repetition time (TR) 2000 ms, flip angle 15°.

2.4. fMRI data analysis

Individual fMRI analyses were performed with the FEAT module, included in the FSL (FMRIB Software Library) software, version 5.0 (Smith et al., 2004). In the pre-processing phase, images were corrected for movement (using the MCFLIRT algorithm), normalised to a common stereotactic space (Montreal Neurological Institute template) and spatially filtered with a Gaussian filter (full-width at half maximum (FWHM) = 5 mm). To minimise unwanted movement-related effects, individuals with an estimated maximum absolute movement greater than 3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

General linear models were fitted to generate whole-brain individual activation maps for each emotion (disgust, fearful, sad, or happiness vs. neutral images) and neutral images (vs. baseline). To further reduce the potential effect of movement, values of movement parameters were included as nuisance covariates in the fitting of individual linear models. Group comparisons were performed at the cluster level with a family-wise corrected *p* value of 0.05 using Gaussian random field methods. The default threshold of *z* = 3.1 was used to define the initial set of clusters. Age, sex and IQ defined by TAP were used as covariates in all analyses.

2.5. Behavioural data analysis

Statistical analyses were performed using SPSS 23.0 (IBM Corp., Armonk, N.Y., USA). We used independent samples *t*-tests to assess differences in the scores (images correctly classified as previously presented or new and emotional intensity) between patients and healthy

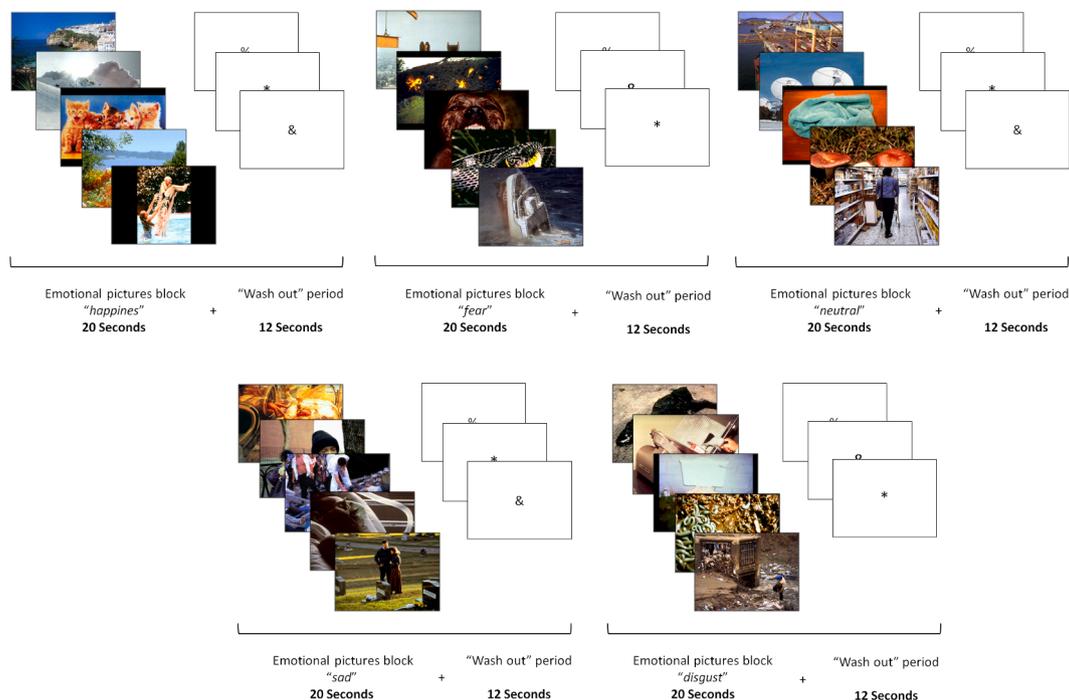


Fig. 1. Five of the 24 blocks presented during the Emotional pictures task, each block represent a different type of emotional scene. Each image (emotional or neutral picture or symbol) was presented for 4 s.

controls. For variables that did not meet the normality assumption (emotional valence, correct classification according to emotional type and type of error in classification according to emotional type), the Mann-Whitney test was used. In relation to emotional intensity we performed a repeated measures ANOVA to assess intra-group differences and post-hoc paired samples *t*-test analysis to assess differences between emotional categories. Additionally, False Discovery Rate (FDR) control was applied as correction for multiple comparisons (Glickman et al., 2014).

3. Results

From the fifty-seven adults with schizophrenia scanned, seven patients were excluded due to excessive head movement and twenty-four due to poor behavioural performance in the post-scanning test (they wrongly classified more than 50% of the images as previously presented or new, indicating that they may not have been paying attention during the task). Patients and controls were matched according to age, sex, and premorbid-IQ (see Table 1). All patients were on antipsychotic treatment: 4 on typical neuroleptics, 17 on atypical neuroleptics, and 5 on both atypical and typical.

3.1. Behavioural data

Patients and healthy controls showed no statistically significant differences in recognizing images presented during the scanning session (i.e., confirming whether they had seen each image or not) in neither emotional category.

Concerning emotional valence, patients scored happy images as less positive ($z = 2.518$; $p = .012$) and sad images as less negative ($z = 2.027$; $p = .043$) than controls.

Concerning emotional intensity, patients rated neutral pictures as more arousing than controls ($t(54) = -3.889$; $p < .001$). There were no statistically significant differences in the rest of the emotional categories presented. The intragroup analysis showed no statistically significant differences in emotional intensity scores between emotional categories in the patient group ($F(3,25) = 1.388$; $p = .256$) or the control group (F

$(3,25) = 1.802$; $p = .167$).

Finally, patients incorrectly classified more pictures than controls in all emotional categories (Table 2). Specifically, they misclassified disgust and sadness as fear ($p < .001$ and 0.007 , respectively). They also tended to categorize neutral images as emotional, i.e., they misclassified them as disgust ($p = .012$), fear ($p = .001$), happiness ($p < .001$), or sadness ($p = .006$) (see Table 3).

When applying FDR adjustment as multiple comparison correction, results with a $p < .015$ survived as statistically significant effects. Tables 2 and 3 show uncorrected *p*-values.

3.2. fMRI data

Mean activations in patients and controls and group differences for each emotional category are summarized below. Detailed areas and MNI coordinates are presented in supplementary material (Tables S1 to S4).

3.2.1. Brain responses to disgust images vs neutral images

3.2.1.1. Within-group responses in the patients and controls. The healthy controls showed activation in left insula, inferior frontal cortex and right dorsolateral prefrontal cortex. There was also activation in visual areas. Activations in subcortical areas included hippocampus, midbrain and thalamus (see Fig. 2A).

The activation pattern in patients was very similar to that of controls, but larger, and including additional activations in the right temporal pole, the amygdala bilaterally and left supramarginal and angular gyrus, and also the medial superior parietal cortex that extended into supplementary motor area. Activation in right prefrontal cortex was also observed, with a larger extension than in controls (see Fig. 2B).

3.2.1.2. Between-group differences. Schizophrenia patients, compared to controls, showed higher activity in the right superior temporal cortex, spanning portions of the middle and inferior temporal cortex (MNI coordinates $x = 66$, $y = -20$, $z = 2$; $Z = 4.07$; cluster size = 358 voxels; $p = 0.001$; see Fig. 2C and Table 4).

Table 2
Behavioral performance of patients and controls.

	Patients (n = 26)	Controls (n = 30)		p
<i>% images correctly classified as previously presented or new</i>				
Total	68.51 (11.73) range 50–87.01	72.86 (11.74) range 51.30–95.45	t = 1.384	0.172
Disgust	74.08 (15.52) range 47.82–100	78.26 (14.39) range 47.83–95.65	t = 1.045	0.301
Fear	71.69 (9.18) range 52–84	73.47 (11.09) range 52–96	t = 0.646	0.521
Happiness	69.37 (11.89) range 50–92.31	72.18 (13.39) range 46.15–96.15	t = 0.822	0.415
Sadness	65.23 (17.78) range 32–96	71.07 (17.82) range 32–96	t = 1.224	0.226
Neutral	65.8 (14.39) range 41.81–90.91	71.45 (14.63) range 38.18–94.54	t = 1.452	0.152
<i>Emotional valence of the images (scored from -1 to 1)</i>				
Disgust	-0.88 (0.15) range -1 to -0.40	-0.91 (0.12) range -1 to -0.55	z = 0.709	0.479
Fear	-0.77 (0.19) range -1 to 0.40	-0.83 (0.16) range -1 to -0.40	z = 1.120	0.263
Happiness	0.62 (0.49) range -0.70 to 1	0.89 (0.18) range 0.15 to 1	z = 2.518	0.012*
Sadness	-0.7 (0.24) range -1 to 0	-0.83 (0.16) range -1 to -0.50	z = 2.027	0.043*
Neutral	0.24 (0.65) range -0.95 to 1	-0.07 (0.64) range -1 to 1	z = 1.816	0.069
<i>Emotional intensity of the images (scored from 0 to 1)</i>				
Disgust	0.50 (0.26) range 0.11–0.98	0.56 (0.19) range 0.10–0.84	t = 0.881	0.383
Fear	0.51 (0.26) range 0.08–0.97	0.54 (0.20) range 0.05–0.89	t = 0.471	0.639
Happiness	0.51 (0.26) range 0.03–1	0.57 (0.16) range 0.26–0.86	t = 1.062	0.295
Sadness	0.46 (0.27) range 0.01–0.98	0.52 (0.19) range 0.07–0.83	t = 1.014	0.315
Neutral	0.32 (0.24) range 0.01–0.89	0.11 (0.11) range 0.003–0.54	t = -3.889	0.001**
<i>% images correctly classified according to the emotional category</i>				
Total	73.07 (12.41) range 45.00–96.67	83.63 (10.07) range 55.83–95.83	z = 3.527	0.001**
Disgust	92.31 (4.64) range 77.50–98.33	95.08 (2.72) range 89.17–100	z = 2.393	0.017*
Fear	92.31 (4.43) range 85–99.17	95.08 (4.32) range 83.33–100	z = 2.513	0.012*
Happiness	89.61 (5.91) range 77.50–99.17	94.94 (3.19) range 86.67–100	z = 3.632	0.001**
Sadness	89.81 (4.91) range 78.33–97.50	93.44 (4.41) range 80.00–99.17	z = 2.887	0.004*
Neutral	82.11 (10.13) range 58.33–99.17	88.72 (9.5) range 59.17v98.33	z = 2.861	0.004*

Note. *Statistically significant at $p < .05$ level; **Statistically significant at $p < .001$ level. Measures are means (SD). Group differences were tested with an unpaired two sample *t*-test for normal distributed data and Mann-Whitney *U* test for non-normal distributed data. $t = t$ value from *t*-test, $z = z$ value from Mann-Whitney *U* test. Uncorrected *p*-values are shown (*p*-values < 0.015 survive FDR correction).

3.2.2. Brain responses to fearful images vs neutral images

3.2.2.1. Within-group responses in the patients and controls. The control group showed a bilateral activation pattern that included the occipital cortex extending dorsally into the temporal and supramarginal cortex and ventrally into the fusiform gyrus. Subcortical activations included right hippocampus and parahippocampus (Fig. 3A).

Patients showed a similar but more extensive activation pattern that also included the whole lateral frontal cortex (bilaterally), the medial superior frontal and the anterior cingulate cortex. Subcortical activations were also more extensive, including bilateral amygdala, bilateral hippocampus and parahippocampus and thalamus (Fig. 3B). Bilateral amygdala was activated as a part of a larger cluster with its peak in the hippocampus (See Table S2 in Supplementary Material).

Table 3
Type of error in image classification according to the emotional category.

% Type of error	Patients (n = 26)	Controls (n = 30)	z	p
Disgust as fear	6.73 (8.48) range 0–30	0.83 (2.3) range 0–10	3.817	0.001**
Disgust as happy	0.96 (2.45) range 0–10	0.5 (1.52) range 0–5	0.645	0.519
Disgust as sad	12.69 (10.31) range 0–35	11.67 (10.2) range 0–35	0.341	0.733
Disgust as neutral	15.78 (15.98) range 0–60	13 (13.81) range 0–60	0.441	0.659
Fear as disgust	2.69 (5.87) range 0–25	2 (3.85) range 0–15	0.095	0.924
Fear as happy	2.5 (5.7) range 0–25	1 (2.75) range 0–10	1.234	0.217
Fear as sad	9.42 (6.53) range 0–20	8.17 (12.35) range 0–50	1.822	0.068
Fear as neutral	15 (21.95) range 0–75	15.67 (20.75) range 0–100	0.861	0.389
Happy as disgust	0.38 (1.36) range 0–5	0 (0) range 0–0	1.533	0.125
Happy as fear	1.15 (3.26) range 0–10	0.33 (1.2) range 0–5	0.731	0.465
Happy as sad	3.27 (6.47) range 0–25	1 (3.05) range 0–15	1.651	0.099
Happy as neutral	17.88 (17.50) range 0–55	17.33 (15.58) range 0–55	0.174	0.862
Sad as disgust	3.85 (9.83) range 0–50	1.33 (2.25) range 0–5	1.533	0.125
Sad as fear	5.38 (7.06) range 0–25	1.5 (3.5) range 0–15	2.699	0.007*
Sad as happy	5.19 (8.77) range 0–40	2.17 (4.68) range 0–15	1.579	0.114
Sad as neutral	14.04 (15.23) range 0–50	11.5 (12.25) range 0–65	0.975	0.330
Neutral as disgust	1.54 (4.9) range 0–25	0.08 (0.45) range 0–2.5	2.504	0.012*
Neutral as fear	1.63 (2.63) range 0–10	0.00 (0.00) range 0–0	3.471	0.001**
Neutral as happy	15.48 (13.94) range 0–50	4 (6.49) range 0–27.5	4.086	0.001**
Neutral as sad	3.65 (4.91) range 0–17.5	1 (2.13) range 0–10	2.774	0.006*

Note. *Statistically significant at $p < .05$ level; **Statistically significant at $p < .001$ level. Measures are means (SD). Group differences were tested with Mann-Whitney *U* test. $z = z$ value from Mann-Whitney *U* test. Uncorrected *p*-values are shown (*p*-values < 0.015 survive FDR correction).

3.2.2.2. Between-group differences. Group comparison results (Fig. 3C) showed higher activations in the patient group in midline regions, from the medial frontal cortex to anterior cingulate cortex, and bilaterally the superior frontal gyrus and in superior and inferior temporal cortex. Patients also presented higher activations in visual areas and cerebellum. Areas and MNI coordinates are detailed in Table 5. Additionally, considering the main role of amygdala in fear processing (LeDoux, 2003) and to further explore amygdala activation in controls and patients, ROIs for the amygdala were defined according to the Oxford-Harvard probabilistic subcortical atlas from FSL. Student's *t*-test showed statistically significant differences between groups at ROI level in both, right ($p = .041$) and left ($p = .016$), amygdala (Fig. 3D), patients showed hyperactivated amygdala response compared to controls.

3.2.3. Brain responses to happy images vs neutral images

3.2.3.1. Within-group responses in the patients and controls. In response to happy images, controls showed activation in middle and inferior temporal cortex and in visual cortex areas (Fig. 4A). Patients showed activation in the same regions, with visual cortex activations extending into right fusiform gyrus and right precentral gyrus. Patients also showed activation in left hippocampus (see Fig. 4B). Results showed no statistically significant differences in activation between both groups.

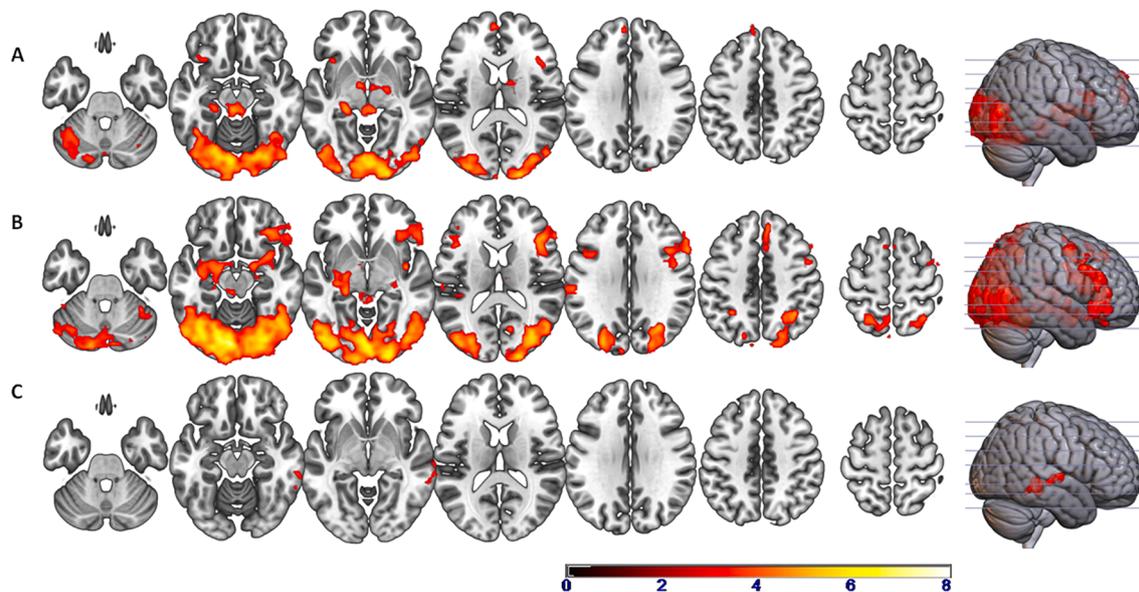


Fig. 2. Areas of significant activation in response to disgust images (relative to neutral images) for controls (A) and patients (B). (C) shows areas of significant differences between patients and controls in this contrast. Colour bar depicts Z values. Images are displayed in neurological convention (right is right).

Table 4
Regions with increased response to disgust images (compared to neutral images) in schizophrenia patients compared to healthy controls.

Region/ Contrast	Hemisphere	MNI coordinates			Z- value	k	p
		x	y	z			
Superior temporal cortex	R	66	-20	2	4.07	358	$p = 0.001$
Medial temporal cortex	R	68	-10	2	4.07		
	R	66	-36	-12	3.91		
	R	68	-34	0	3.62		
Inferior temporal cortex	R	62	-46	-12	3.77		
Rolandic operculum	R	66	-44	-10	3.58		

3.2.4. Brain responses to sad images vs neutral images

3.2.4.1. Within-group responses in the patients and controls. In response to sad images, controls presented activations in right inferior frontal cortex and medial superior frontal cortex, visual cortex and cerebellum that extended to posterior cingulate cortex and precuneus and to inferior and middle temporal cortex. Subcortically controls showed activations bilaterally in thalamus, basal ganglia and left hippocampus and parahippocampus (Fig. 5A).

As shown in Fig. 5, patients showed an activation pattern very similar to controls but less extensive, activations were not observed in medial and superior frontal cortex. Patients also showed activation in right precentral gyrus and subcortically in left amygdala. Results showed no statistically significant differences in activation between both groups.

Brain responses to neutral images have been included in [Supplementary material](#) (see [Supplementary Results, Fig. S1 and Table S5](#)).

Additionally, we explored the relationship between key brain regions involved in fear and disgust processing in schizophrenia (those showing differences between patients and controls) and behavioral performance and schizophrenia symptoms. For this purpose, we analyzed the

correlation between the mean activation for each cluster of hyperactivation in patients in response to fear and disgust images, and intensity and valence scores for the same emotional category, and also with main syndromes of the PANSS: negative, positive and disorganized, based on factor analysis (Wallwork et al., 2012). Results showed no statistically significant correlation between any of the variables included.

4. Discussion

The present study is one of only a few to examine brain activations in schizophrenia to scenic emotional images and is the first to examine the emotions of fear, disgust, happiness, and sadness separately. The main findings were that, at the behavioral level, patients with schizophrenia misclassified more negative emotional images (disgust and sadness) than the controls, and they also misclassified more neutral images as emotional. At the level of brain responses, schizophrenia patients significantly differed from controls in images eliciting disgust and fear, but not sadness or happiness. Patients and controls did not differ in brain responses to neutral images, used as baseline to compare brain responses to emotional categories. In response to disgust, the patients hyperactivated the right temporal cortex. In response to fear, they showed heightened activation in midline regions, from the medial frontal cortex to the anterior cingulate cortex, as well as in the superior frontal cortex bilaterally and parts of the temporal cortex and the visual cortex.

Behaviorally, patients in our study made significantly more errors in emotion categorization in relation to negative emotions (i.e. classifying sadness and disgust as fear), and for neutral images (i.e. classifying these as emotional). This contrasts with Takahashi et al. (2004), who found no differences between patients and controls when categorizing stimuli as negative, positive, or neutral. Concerning arousal, we found that schizophrenia patients rated neutral images as more arousing than controls, a finding also reported by Pankow et al. (2013). However, these previous studies only differentiated between positive and negative stimuli, not between emotional categories, so valence rating differences and classification errors between different negative emotions might have been overlooked. Finally, we found that the patients rated sad images as less negative, and happy images as less positive than controls. Clearly, abnormalities in rating the emotionality of scenes in schizophrenia are complex, and the pattern cannot be considered to have been fully established by the few studies carried out to date. On the other

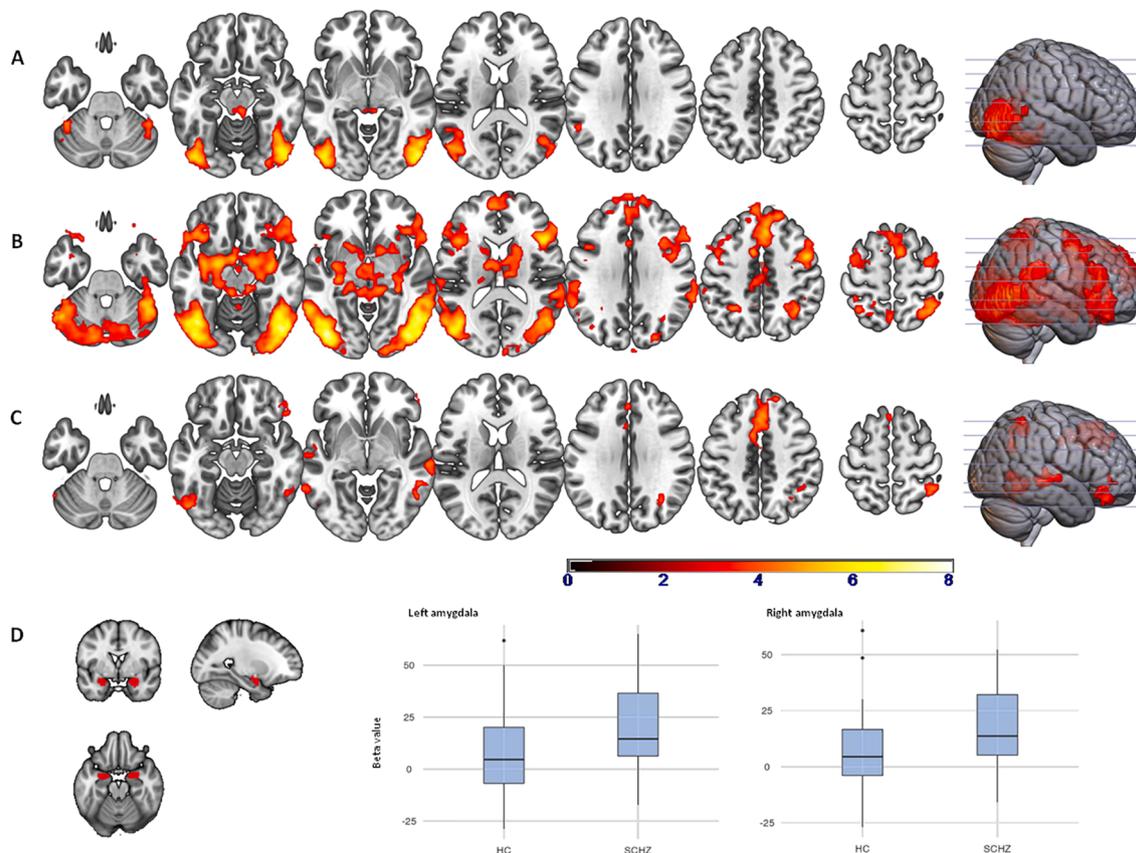


Fig. 3. Areas of significant activation in response to fearful images (relative to neutral images) for controls (A) and patients (B). (C) shows areas of significant differences between patients and controls in this contrast. Colour bar depicts Z values. Images are displayed in neurological convention (right is right). (D) shows anatomically-defined ROIs for the amygdala and the boxplot for activation levels (beta values) in patients and controls for left and right amygdala in response to fearful images, for illustrative purposes. The ROIs were defined according to the Harvard-Oxford probabilistic subcortical atlas from FSL.

Table 5

Regions of increased activation in response to fearful images (compared to neutral images) in schizophrenia patients compared to healthy controls.

Region/Contrast	Hemisphere	MNI coordinates			Z-value	k	p
		x	y	z			
Supplementary motor area	L	0	22	48	5.18	1434	$p < 0.001$
Superior frontal gyrus	R	4	28	42	4.93		
	L	-4	32	58	4.26		
Cingulum	L	-8	6	44	4.57		
Superior temporal gyrus	L	-66	-12	4	4.3		
Precentral gyrus	L	-4	32	58	4.26		
Middle temporal gyrus	L	-60	-18	2	3.88		
Rolandic operculum	L	-52	4	12	3.88		
Inferior frontal gyrus	L	-40	18	16	3.57		
Caudate	R	20	-8	22	3.39		
Cerebellum	L	-52	-56	-34	4.54	544	$p < 0.001$
Inferior parietal cortex	R	42	-50	56	4.62	482	$p < 0.001$
Middle temporal cortex	R	52	-58	0	4.99	403	$p < 0.001$
Inferior frontal gyrus	R	46	40	-22	4.67	398	$p < 0.001$
Superior temporal gyrus	L	-66	-12	4	4.3	343	$p = 0.001$
Middle temporal gyrus	R	64	-24	-2	4.65	295	$p = 0.004$

hand, it seems possible that some of the findings may be understandable in terms of an ‘aversive bias’ found by [Cohen and Minor \(2010\)](#) in a meta-analysis of studies that induced emotional states in schizophrenic patients using various techniques, including visual stimuli (faces, pictures and film clips), valenced words, flavored liquids, and social interactions. This meta-analysis found that patients with the disorder tended to report aversive responses in response to both positive emotion-inducing stimuli and neutral stimuli.

Viewing of emotional scenes was associated with altered, specifically

increased brain activation in patients in the case of two emotions, disgust, and fear. Inconsistent results have been found in the three previous studies using scenic stimuli to date. [Takahashi et al. \(2004\)](#) initially found reduced activation in the right amygdala, bilateral hippocampal regions, the prefrontal cortex, the left putamen and caudate, the left posterior thalamus, and visual areas in patients when they viewed negative images. [Pankow et al. \(2013\)](#) also found amygdala hyperactivation in response to negative images in schizophrenia, while [Hägele et al. \(2016\)](#) found no differences between different diagnostic

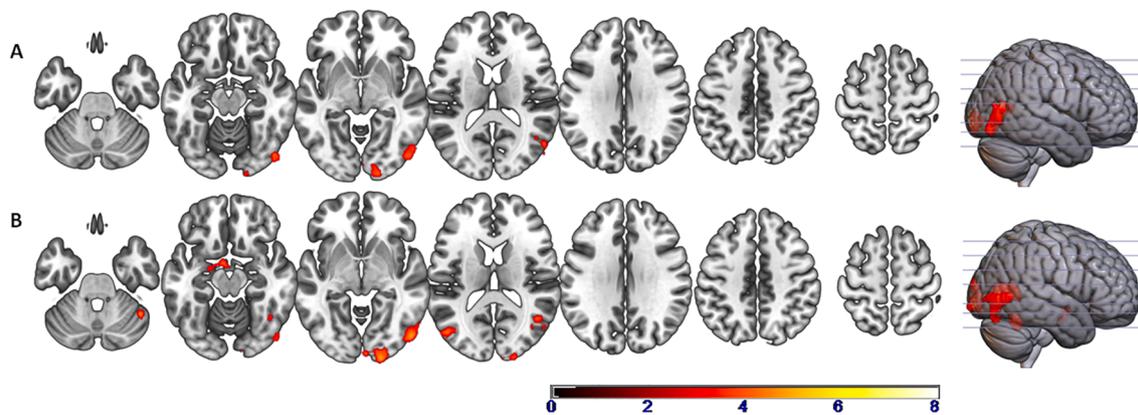


Fig. 4. Areas of significant activation in response to happy images (relative to neutral images) for controls (A) and patients (B). Colour bar depicts Z values. Images are displayed in neurological convention (right is right).

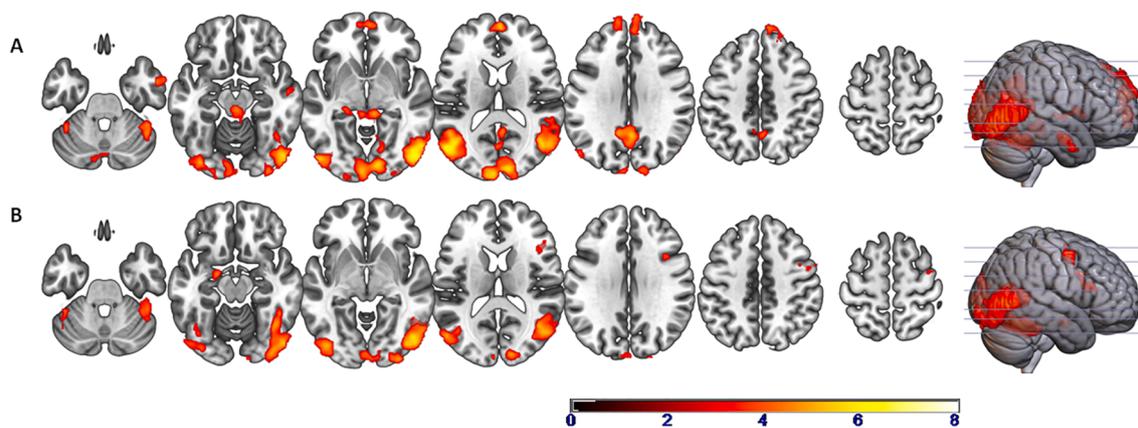


Fig. 5. Areas of significant activation in response to sad images (relative to neutral images) for controls (A) and patients (B). Colour bar depicts Z values. Images are displayed in neurological convention (right is right).

groups, including schizophrenia, and healthy controls, in activations to negative images. In our study there were no significant differences in amygdala activation between groups in the whole-brain analysis; however, it is interesting to note that, when using an ROI in the amygdala, significant differences were found on both the right and left in response to fear scenes, with once again the patients showing increased activation in comparison to healthy controls. Also, patients showed a hyperactivated response to fear images in prefrontal areas, but hyperactivated right temporal areas in response to disgust images. This, again, highlights that the use of wide categories, like negative and positive emotions, might not reflect the actual brain responses to different emotions and mask altered patterns of activation that arise in response to more specific stimuli. Research using emotional faces has actually examined brain responses to specific emotional categories, mostly in relation to fear in the case of schizophrenia.

Few studies have used facial stimuli to examine responses to disgust, and results showed hypoactivation in prefrontal areas, insula, and hippocampus (Lindner et al., 2016; Williams et al., 2007). On the other hand, studies about fear processing in schizophrenia have shown a link between fear processing and the activity of prefrontal areas, the hippocampus, the amygdala, and visual areas (Hall et al., 2008; Li et al., 2012; Lindner et al., 2016; Szabó et al., 2017; Williams et al., 2007; Williams et al., 2004), a pattern similar to what we found in fear scenic stimulus processing. However, the direction of the alterations diverges: some studies found hyperactivation in these regions in schizophrenia patients (Lindner et al., 2016; Liu et al., 2011; Rauch et al., 2010; Williams et al., 2004), while others found hypoactivation (Hall et al., 2008;

Szabó et al., 2017; Williams et al., 2007), or no differences between schizophrenia patients and healthy controls (Holt et al., 2005). Although we found some similar regions to that found using faces involving brain responses to emotional scenes, differences in brain responses to scenes and faces are noteworthy. Face processing involves, besides the face recognition process, the emotion identification in others' faces (Ellis and Young, 1988; Haxby et al., 2000; Calder & Young, 2005). However, scenes would act as an evocative stimulus (Takahashi et al., 2004), that might activate as well autobiographical memories to interpret the scene. Therefore, brain responses for emotional processing would be different to scenes and faces.

The regions we found to be hyperactivated in response to disgust in schizophrenia, involving temporal cortex areas, have also been found to be involved in disgust processing in healthy subjects in previous meta-analyses (Murphy et al., 2003; Phan et al., 2002; Wager et al., 2015). The most recent meta-analysis, an activation likelihood estimation (ALE) meta-analysis (Kirby and Robinson, 2017) using the BrainMap database, has intended to create an activation map for different emotions. The disgust map included the temporal cortices, along with other regions (cingulate, postcentral gyrus, thalamus, putamen and insula) that were unaltered in our patients. It must be noted, though, that we used scenic stimuli, a category underrepresented in the previous meta-analyses.

Similar to disgust, the pattern of activations found in patients in response to fear images included regions normally found to be involved in fear processing in healthy subjects, although with larger extension and intensity. Two early meta-analyses (Murphy et al., 2003; Phan et al., 2002) including studies using a wide range of stimuli (e.g. words,

vocalizations, faces, olfactory stimuli, IAPS pictures) found that, although the activation patterns differed along studies, the amygdala was consistently associated with fear processing. More recently, a meta-analysis by Wager et al. (2015) showed that fear processing mainly involved cognitive control networks (dorsal attention and frontoparietal), limbic, default-mode and occipital networks. The fear map built by Kirby & Robinson (2017) included cortical areas that were very similar to those hyperactivated in schizophrenia in the present study, in addition to limbic areas like the amygdala or the hippocampus.

Only one previous study used scenic stimuli including the same emotional categories used in the present work (Radua et al. 2014), which examined brain responses to images evoking happiness, sadness, fear and disgust in healthy individuals. Regarding disgust images, the regions that patients hyperactivated in the present study included the temporal cortex, a region found to deactivate in response to disgust images in healthy adults (Radua et al. 2014). In that study, processing of fear images was associated with activity in the visual cortex, amygdala and hippocampus, thalamus, temporal and lateral prefrontal cortex, which partially coincide with the hyperactive regions in schizophrenic patients observed in the present work in response to fear images.

The reason why differences appeared for disgust and fear images, but not for happiness and sadness, might be linked to the fact that disgust and fear are emotions characterized by a negative valence and a high arousal, in contrast to sad images, the other negative emotional category studied, characterized by a low arousal. This hyperactivation in response to high arousal negative images might reflect a bias toward potentially harmful emotions. Bias was also present in behavioral responses: patients showed a tendency to misclassify negative emotions as fear, although they also rated fear images as less negative, which contrasts with the hyperactivated brain responses to those images. Previous studies have pointed out a link between positive symptoms like paranoia and an attentional bias to threat-related material using faces (Bentall and Kaney, 1989; Green et al., 2003; Phillips et al., 2000). This bias was explained by Frith and Corcoran (1996) as caused by deficits in theory of mind, the so-called ‘over-mentalizing’ in patients with positive symptoms, and by Green and Phillips (2004), who linked paranoia to misperception of ambiguous facial expressions as threatening. In a similar line, our results suggest that patients with schizophrenia might display a hyper-reactivity to negative, threatening stimuli even without the social/facial expression component.

This study has some limitations. First, the sample sizes of the present study are relatively small. Although previous studies have smaller samples sizes and our results constitute an important advance, this might have influenced the power of the study in detecting differences in group comparisons and limited the generalizability of results. Cognitive deficits in patients make also more difficult the study of emotional processing, therefore only patients who have shown to be attentive during the whole task have been included in the analysis. Although we are not able to ensure that poor performance is due to lack of attention instead of a memory problem, according to previous research schizophrenia patients show intact priming in a perceptually driven task, similar to that used in our study (Spataro et al., 2016), while impairments in sustained attention have been described as central to schizophrenia (Green et al., 2000). Therefore, probably, most patients presented a deficit in attention during the task rather than a memory problem. The use of this criteria has considerably reduced the sample size but also made the results more reliable. Second, in our study all the participants in the patient group were taking antipsychotics; medication role in brain responses to external stimuli is still unknown, so a higher control of this variable would be recommended. Third, as in most schizophrenia research, women are underrepresented. It should be considered that emotional processing in women might be different to men, so it would be necessary for future research to study sex differences in emotional processing in schizophrenia. Finally, it should be noted that IAPS was developed to evaluate valence and arousal, rather than the response to specific emotions. A new set of scenic emotional images,

specifically developed to evaluate the response to specific emotions, would probably further clarify the common and specific components of their associated brain responses, and help to identify the alterations in emotional processing in psychiatric disorders. For future research, it would be also interesting to study brain responses to emotional scenarios with higher ecological validity, i.e., using virtual reality technology. This would allow controlling different components of the situation and the interaction with the scenario (e.g., studying the response to neutral social stimuli in a threatening scenario or vice-versa).

Results found by this study contribute to the emotion processing literature in schizophrenia by demonstrating altered brain responses to specific emotions, fear and disgust, accompanied by a biased behavioral response to fear. The abnormal processing of potentially harmful emotions in schizophrenia pointed out by these results contributes to the understanding of positive symptoms supporting Frith and Corcoran’s proposal on altered theory of mind in schizophrenia. As well, the understanding of neural correlates of schizophrenia symptoms provides valuable information for the development of new treatments, pharmacological or others, like neuromodulation. And the improvement of clinical intervention oriented to manage positive symptoms, like psychoeducation, by focusing on this bias to threatening stimuli. Furthermore, this paradigm would let to evaluate the efficacy of clinical intervention. If we consider hyperresponse to threaten stimuli a main characteristic of brain malfunction in schizophrenia related to positive symptoms, one could expect that effective interventions to reduce positive symptoms would reduce brain hyperactivity as well in response to specific emotions.

To sum up, this is the first study to investigate brain responses to pictures selected to elicit specific emotions in schizophrenic patients. This approach has led to identify a response pattern in schizophrenia characterized by a bias to threatening stimuli in both behavioral and brain responses. Specifically, patients tended to misclassify negative images as depicting fear, and their brain response to fear images was characterized by a hyperactivation of fear-related areas. Similarly, the patients’ response to disgust images was also characterized by hyperactivation in some of the regions previously found to be involved in disgust processing in healthy controls. Our results indicate that scenic emotional processing in schizophrenia is characterized by a bias towards threat-related emotions and a hyperreactivity to disgust- and fear-evoking stimuli, that is manifested through the hyperactivation of the brain regions involved in processing these emotions.

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CRediT authorship contribution statement

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Writing – review & editing. **Francisco Portillo:** Investigation, Resources, Writing – review & editing. **Jordi Ortiz-Gil:** Investigation, Resources, Writing – review & editing. **Silvia Alonso-Lana:** Investigation, Resources, Writing – review & editing. **Teresa Maristany:** Investigation, Resources, Writing – review & editing. **Joaquim Radua:** Conceptualization, Writing – review & editing, Funding acquisition. **Raymond Salvador:** Data curation, Writing – review & editing, Supervision, Funding acquisition. **Salvador Sarró:** Resources, Data curation, Writing – review & editing, Supervision. **Edith Pomarol-Clotet:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2021.102894>.

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