Increased fusiform area activation in schizophrenia during processing of spatial frequency-degraded faces, as revealed by fMRI

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Background. People with schizophrenia demonstrate perceptual organization impairments, and these are thought to contribute to their face processing difficulties.

Method. We examined the neural substrates of emotionally neutral face processing in schizophrenia by investigating neural activity under three stimulus conditions: faces characterized by the full spectrum of spatial frequencies, faces with low spatial frequency information removed [high spatial frequency (HSF) condition], and faces with high spatial frequency information removed [low spatial frequency (LSF) condition]. Face perception in the HSF condition is more reliant on local feature processing whereas perception in the LSF condition requires greater reliance on global form processing. Past studies of perceptual organization in schizophrenia indicate that patients perform relatively more poorly with degraded stimuli but also that, when global information is absent, patients may perform better than controls because of their relatively increased ability to initially process individual features. Therefore, we hypothesized that people with schizophrenia (n = 14) would demonstrate greater face processing difficulties than controls (n = 13) in the LSF condition, whereas they would demonstrate a smaller difference or superior performance in the HSF condition.

Results. In a gender-discrimination task, behavioral data indicated high levels of accuracy for both groups, with a trend toward an interaction involving higher patient performance in the HSF condition and poorer patient performance in the LSF condition. Patients demonstrated greater activity in the fusiform gyrus compared to controls in both degraded conditions.

Conclusions. These data suggest that impairments in basic integration abilities may be compensated for by relatively increased activity in this region.

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Introduction

Schizophrenia patients have demonstrated impairments in both behavioral performance and psychophysiological activation, as measured by event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI), when processing facial stimuli (Dong et al. 2006; Herrmann et al. 2006; Yoon et al. 2006; Chen et al. 2008a, b; Fakra et al. 2008). These impairments, which may be causal factors in the social cognitive and interpersonal difficulties in schizophrenia (Turetsky et al. 2007; Anilkumar et al. 2008; Green et al. 2008), may reflect more basic visual processing impairments (Chen et al. 2008a, b). For example, schizophrenia patients have demonstrated impaired perceptual organization (Phillips & Silverstein, 2003; Uhlhaas & Silverstein, 2005), or the ability to effectively process global form information, and this has been linked to poorer face perception abilities (Frith et al. 1983; Turetsky et al. 2007). In addition, compared to controls, schizophrenia patients demonstrate less of a change in face processing performance after global form information is removed, suggesting that patients are more reliant on feature-based processing of faces (Joshua & Rossell, 2009). Schizophrenia patients have also demonstrated difficulties with low spatial frequency processing (O’Donnell et al. 2002; Kiss et al. 2006), which may impact the processing of multi-frequency stimuli such as faces. The fusiform face area (FFA) has been
identified as an essential area for face recognition, where pathways that process disparate information related to, for example, face form and gender converge to allow for face processing (Kanwisher, 2004; Price & Friston, 1999). Although the FFA has been shown to function normally in schizophrenia in general face recognition (Yoon et al., 2006), it has been found to have an abnormal structure in some people with schizophrenia, and this has been linked to face memory performance (Highley et al., 1999; Lee et al., 2002; Onitsuka et al., 2003). In a recent fMRI study (Silverstein et al., 2009), for schizophrenia patients the fusiform area was more activated when processing shape stimuli where contour fragment orientations were decorrelated compared to when processing more intact stimuli, in the context of reduced activation in earlier cortical areas normally associated with integrative form processing (e.g. V2, V3, V4). The opposite pattern was found in the control group. This is evidence that fusiform activity in schizophrenia may be enhanced when impaired perceptual organization processes lead to degraded representations reaching this higher cortical area.

Studies of facial recognition in humans suggest that mid-spatial frequencies are crucial for efficient facial recognition (Hayes et al., 1986), and removal of mid-frequency data has been shown to lead to decreased facial recognition performance (Fiorentini et al., 1983a, b; Costen et al., 1996). However, when forced to rely on either high or low frequency data alone for identification, healthy adults and children above 8 months of age tend to rely on low spatial frequency information, which may represent a tendency to initially encode the global structure of the face to determine identity (Tanaka & Farah, 1993; Costen et al., 1996; Schwarzer & Zauner, 2003; Deruelle & Fagot, 2005). As noted above, however, the ability to process low frequency/global form information is reduced in schizophrenia.

In this study, we examined the effects of spatial frequency manipulations on emotionally neutral face processing in people with schizophrenia in the context of performing a gender-discrimination task. We chose a gender-discrimination task for several reasons, including: (1) gender discrimination is a relatively simple task and is therefore unlikely to introduce confounds from a generalized deficit, reduced motivation and/or anxiety due to failure experiences (Deruelle & Fagot, 2005); (2) if faces are not repeated, there is no learning and/or memory component in the task; (3) ERP studies in humans and monkeys demonstrate that gender discrimination tends to occur separate from and faster than the structural encoding responsible for detection of identity or expression (Bruce et al., 1987; Mouchetant-Rostaing et al., 2000; Mouchetant-Rostaing & Giard, 2003); and (4) gender processing does not seem to interfere with detection of either facial features or global processing of faces (Mouchetant-Rostaing & Giard, 2003). Therefore, in theory, a gender-discrimination task is an appropriate choice to ensure participant engagement during a fMRI session examining other aspects of face processing.

We manipulated the spatial frequency composition of faces to increase the salience of global form or local contour. Removal of low spatial frequency information from neutral faces [high spatial frequency (HSF) condition] was predicted to increase the reliance on local feature processing during face perception, whereas removal of high spatial frequency information [low spatial frequency (LSF) condition] requires greater reliance on global form processing. Past studies of perceptual organization in schizophrenia indicate that patients perform more poorly with degraded stimuli, but studies also show that when global information is absent (which is detrimental to performance for controls), patients may perform better than controls because of their relatively increased ability to process individual features early in visual processing (e.g. Place & Gilmore, 1980; reviewed in Uhlhaas & Silverstein, 2005). Therefore, we hypothesized that: (1) people with schizophrenia would show differential brain activation during both the HSF condition and the LSF condition compared to controls; and (2) patients would show less of a performance deficit, and perhaps a superiority, relative to controls in the HSF condition, compared to the LSF condition.

Method

Subjects

The sample consisted of 14 people with schizophrenia (nine men) and 13 healthy control subjects (three men). Schizophrenia patients were enrolled either in a partial hospital program or in an outpatient program. The groups were matched on age, education and maternal education levels. All subjects completed a practice version of the task, and were familiarized with the scanning environment (using a mock scanner) the day before the fMRI session. At that session, all patients were interviewed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), which was scored using a five-factor model, including positive, negative, cognitive, excitement, and depression symptoms (Lindenmayer et al., 1994). Medication level was assessed for patients using published conversion formulas (Woods, 2003) to generate chlorpromazine (CPZ) equivalent daily doses for second-generation antipsychotic medications. All subjects were tested at the MRI Center at the University of Illinois at Chicago.
This group of subjects also completed a contour integration task, and these data are reported in Silverstein et al. (2009). The contour integration task was a two-alternative forced choice task involving determination of the direction that the contours pointed in (left or right), and this was completed during the same scanning session, prior to administration of the face processing task. Notably, that task did not involve face processing, and it could not be performed successfully by local feature analysis.

Stimuli

The task was built in FlashMX and displayed in the scanner using a shielded projector. Stimuli were black-and-white photographs of emotion-neutral faces taken from the Nim Stim facial database (Tottenham et al. 2002). Background information was removed although the hair remained. There was a good distribution of different genders and ethnicities although there were not enough images to completely balance race and gender for all conditions. Represented groups include Black Males, White Males, Asian Males, Black Females, White Females and Asian Females. The stimulus conditions were normal or broad spatial frequency (BSF) faces (unmanipulated images), HSF faces, which contained only images with low frequency signals removed, and LSF faces, which contained only images with high frequency signals removed. The spatial frequency content in the original images was filtered using the Image Processing Toolkit and PhotoshopCS (Adobe, USA). Images were transformed into fourier space and thresholded with a bilevel threshold tool. LSF images were thresholded to 21 cycles/pixel and HSF images were thresholded to 5 cycles/pixel. Images were then smoothed using a Gaussian blur of one pixel and were converted back into image space. An example stimulus from each condition is shown in Fig. 1.

Task

Functional imaging followed a block design with stimuli blocked by condition, with three ‘active’ blocks (one for each condition BSF, HSF and LSF), each lasting for 105 s with 70 brain volumes acquired, separated by 15-s ‘rest’ blocks with a central fixation and 10 volumes acquired. The task began with two ‘rest’ blocks and then ended on a ‘rest’ block. The initial ‘rest’ block was included to allow a period of adaptation and was excluded from the analysis. The central fixation condition was included to allow the hemodynamic response function to return to baseline so that the response to one active condition did not affect the following condition. The three active conditions followed the same order for all subjects: BSF, HSF and LSF. In each active condition, 40 faces were displayed, each for 1500 ms. Subjects were asked to indicate gender by pressing one of two buttons on a standard button box. Responses and latencies were recorded automatically and sent to an Access database.

Brain imaging

All images were acquired using a 3.0-Tesla whole-body scanner (Signa VHi, General Electric Medical Systems, USA). Functional images were acquired first, with the scanner performing serial gradient echo, echo-planar imaging [epiRT, plane = axial, repetition time (TR) = 1499 ms, echo time (TE) = 30.7 ms, flip angle = 90°, matrix = 64 × 64, field of view (FOV) = 20 cm², voxel size = 3.125 × 3.125 × 5 mm, number of excitations (NEX) = 1, bandwidth = 62 kHz]. The duration of the functional acquisition was 6.5 min, during which 25 slices (slice thickness/gap = 4/0 mm) were acquired per volume with a total of 260 brain volumes. The functional paradigm was then followed by acquisition of a high-resolution three-dimensional (3D) inversion recovery fast spoiled gradient recalled echo.
sequence (SPGR, plane = axial, TR = 9 ms, TE = 2.0 ms, flip angle = 25°, NEX = 1, bandwidth = 15.6 kHz, acquisition matrix = 256 × 256, FOV = 22 × 16.5 cm², slice thickness/gap = 1.5/0 mm/mm, slices = 124). The paradigms were presented in the scanner and coordinated with behavioral measurements by a custom-designed MRI synchronization control system. All scan sessions were conducted between 09:00 and 12:00 hours.

Image preprocessing and analysis

Functional MRI analysis was conducted using Statistical Parametric Mapping (SPM2, 2005). Data from each individual subject were initially corrected for head motion and none exceeded one voxel size (3.125 mm) of in-plane motion. The functional data were then co-registered with the corresponding anatomical images, which were then spatially normalized to the Montreal Neurological Institute (MNI) template. The normalized functional data were smoothed with a 9-mm Gaussian smoothing kernel that was approximately three times the original voxel dimensions.

The preprocessed functional data for each individual were then analyzed with a general linear model using three experimental regressors corresponding to each condition the faces were presented in (BSF, LSF, HSF). The onset times of these regressors were convolved with the hemodynamic response function (HDF). Random effects analyses were then conducted on the activation maps for the 27 subjects so that a group activation map could be extracted to each condition the faces were presented in (BSF, LSF, HSF). The onset times of these regressors were convolved with the hemodynamic response function (HDF). Random effects analyses were then conducted on the activation maps for the 27 subjects so that a group activation map could be extracted to identify significant effects across regions for each appropriate statistical contrast. To correct for multiple comparisons on the image data, a false discovery rate (FDR) of 0.05 was applied to all contrasts (Genovese comparisons on the image data, a false discovery rate appropriate statistical contrast. To correct for multiple comparisons on the image data, a false discovery rate (FDR) of 0.05 was applied to all contrasts (Genovese et al., 2002).

After the data were preprocessed to remove the linear trend, correct for head motion, and transformed into normalized space, voxel-wise comparisons were made between the BSF, HSF and LSF conditions and between the control and patient groups. These comparisons were used to identify the networks that were activated, and to examine any gross changes between conditions and between groups in clusters of activation.

In addition to the random effects analyses, correlations were performed to examine the relationship between fMRI activation and behavioral performance. To reduce the potential effects of false-positive findings, which can occur using a whole-brain exploratory voxel-wise correlation approach, we limited our target regions to those that were identified in the above described group analyses. In other words, peak signal change for each subject was extracted from only those brain regions where significant differences existed between patients and controls.

Results

Demographic data

The patient and control groups did not differ significantly in age [mean (s.d.) 32.62 (8.92) vs. 30.46 (6.55) years, t(24) = 0.70, p > 0.49], education level [14.27 (3.30) vs. 15.69 (3.45) years, t(24) = −0.18, p > 0.97], maternal education [13.46 (2.90) vs. 13.42 (2.11) years, t(23) = 0.04, p > 0.97] or paternal education [13.54 (2.60) vs. 14.67 (2.61) years, t(26) = −1.36, p > 0.29]. There was a significant group difference on gender composition [χ²(1) = 4.64, p < 0.05].

Clinical variables

Thirteen of the 14 patients were taking antipsychotic medication. For these patients, the mean daily dose in CPZ equivalents was 353.85 mg (s.d. = 193, minimum = 100, maximum = 700). Mean symptom ratings on the five PANSS factors were as follows: Positive = 2.92 (mild), Negative = 2.63 (minimal to mild), Cognitive = 2.08 (minimal), Excitement = 2.04 (minimal), and Depression = 2.65 (minimal to mild). Because of this low level of symptoms (i.e. restricted range), we did not calculate correlations between symptom levels and behavioral or fMRI indices.

Performance/behavior data

We calculated two 2 × 3 mixed model analyses of variance (ANOVAs), with group (schizophrenia and control) as the between-groups variable, condition (BSF, HSF and LSF) as the repeated-measures variable, and gender discrimination accuracy (percentage correct) and reaction time (RT) as the dependent variables, to test the hypothesis that performance differences between the two groups would vary across condition. Figure 2 displays the behavioral results. For accuracy, the main effect for group was not significant [F(1, 25) = 0.06, p = 0.94]. However, there was a significant main effect for condition [F(2, 50) = 48.47, p < 0.05] and a trend toward a significant condition × group interaction [F(2, 50) = 2.51, p = 0.09]. Simple effects testing of this interaction trend showed that, as predicted, patients performed (non-significantly) better in the HSF condition [schizophrenia = 0.74 (0.18), control = 0.69 (0.13), t(24) = −0.97, p = 0.34] and (non-significantly) worse in the LSF condition [schizophrenia = 0.83 (0.12), control = 0.89 (0.06), t(19) = 1.68, p = 0.12]. The two groups were equivalent in their performance in the BSF condition
[schizophrenia = 0.97 (0.03), control = 0.97 (0.04),
t(24) = 0.22, p = 0.83]. For RT, the main effect of group was not significant [F(1, 25) = 1.80, p > 0.19]. The main effect of condition was significant [F(2, 50) = 25.77, p < 0.001] but the group × condition interaction was not [F(2, 50) = 0.92, p > 0.40].

fMRI activation

Two types of analyses were conducted on the fMRI data. First, the two groups were compared in each condition. These tests represent group differences in the contrasts between each of the HSF, BSF and LSF conditions and the fixation condition (i.e. baseline contrasts). Second, contrasts were calculated between the HSF and BSF condition and between the LSF and BSF condition to examine changes in activation relative to a normal face (i.e. between-condition contrasts). Activation maps for contrasts between controls and patients with schizophrenia are presented in Fig. 3. Coordinates of peak activation for the first set of (baseline) contrasts are presented in Table 1.

BSF condition relative to fixation (Fig. 3, rows A and B)

Clusters of increased activation for controls relative to patients were observed bilaterally in the middle frontal gyrus, thalamus and caudate nucleus. Additional clusters of activation were observed in the left inferior parietal lobule and left parahippocampal gyrus. Additionally, activation was observed along midline structures including the body and posterior aspects of the cingulate gyrus. By contrast, patients showed increased activation relative to controls bilaterally in the superior parietal lobules and also in the anterior and body portion of the cingulate gyrus.

HSF condition relative to fixation (Fig. 3, rows C and D)

Greater activation was observed for controls relative to patients in subcortical structures (the anterior portion and body of the cingulate gyrus, lentiform nucleus, and portions in the thalamus) and the insula. By contrast, patients showed increased activation in cortical areas: the middle frontal gyrus, middle temporal gyrus and in the fusiform gyrus.

LSF condition relative to fixation (Fig. 3, rows E and F)

Controls demonstrated greater activation relative to patients in the middle and inferior frontal gyri, bilaterally in the middle temporal gyri, in both the left and right insula, and in the right parahippocampal gyrus. Patients showed clusters of significant voxels in the left middle temporal gyrus and in the left fusiform gyrus.

HSF condition relative to BSF condition (Fig. 3, rows G and H)

Controls demonstrated greater activation than patients in the HSF condition (relative to BSF) in the eye fields, superior parietal, anterior cingulate and anterior temporal cortices, and the caudate. There was also increased activity bilaterally in the cerebellum (not shown). Patients were more active in the middle frontal gyrus, a portion of the anterior cingulate, and early visual cortex areas (V1–V3).

LSF condition relative to BSF condition (Fig. 3, rows I and J)

As with the HSF-BSF contrast, controls demonstrated more activation than patients in the eye fields, superior parietal, anterior cingulate and anterior temporal cortices, and the caudate. However, with
this contrast, controls also demonstrate significantly greater activity than patients in early visual cortex regions. Patients were more active than controls in other occipital regions, including middle temporal gyrus, and in the fusiform gyrus.

**Correlations between medication dose and behavioral performance**

There was a significant positive correlation between HSF accuracy and CPZ equivalent medication dose ($r = 0.59, p < 0.05$), and a trend towards significance for the correlation between BSF accuracy and dose ($r = 0.51, p < 0.08$). The correlation between medication dose and LSF accuracy was not significant ($r = 0.14, p = 0.65$). Correlations between medication dose and RT for these three conditions were not significant ($r = -0.21, p = 0.50$), BSF ($r = 0.03, p = 0.92$), LSF ($r = -0.17, p = 0.58$). All of these reported $p$ values are uncorrected. None of the above correlations would be statistically significant if a Bonferroni correction is used to control for joint $\alpha$.

**Discussion**

Past studies in schizophrenia have demonstrated impairments in the processing of faces, although the factors responsible for this remain elusive. One hypothesis involves abnormal activity in face processing areas. However, data suggesting the involvement of earlier factors come from recent studies indicating normal fusiform gyrus activity in schizophrenia (Yoon et al., 2006; Anilkumar et al., 2008) and data indicating the role of abnormal perceptual organization as a contributory factor in inefficient face processing (e.g. Frith et al., 1983; Turetsky et al., 2007; Shin et al., 2008), although patients are not completely unable to utilize configural information (Schwartz et al., 2002). Normally, configural information is crucial for initial analysis of face information (Schwarzer & Zauner, 2003), and this information about global form is best represented by information at low spatial frequencies (Costen et al., 1996; Goffaux & Rossion, 2006). It has also been demonstrated that the face identification system responds preferentially to LSF inputs (Rolls et al., 1987; Dailey & Cottrell, 1999; Schyns & Oliva, 1999), and that LSF data are processed earlier than HSF data. Therefore, we hypothesized that patients with schizophrenia would demonstrate poorer performance in processing faces made up primarily of LSF information. By contrast, some prior studies of perceptual organization deficits in schizophrenia (reviewed in Uhlhaas & Silverstein, 2005) noted...
superior processing of feature information compared to controls in conditions that lacked global structure, as a consequence of an ability to rapidly initiate feature processing uninhibited by the (normal) presence of perceptual organization processes. We therefore hypothesized that patients would demonstrate superior task performance in the HSF condition, in which global information is largely absent. The behavioral data indicated a trend towards a group × condition interaction. However, the simple effects

Table 1. Magnitude of peak activity (maximum z statistic) and coordinates in MNI space for each significant cluster of activation.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Contrast</th>
<th>Region</th>
<th>Hemisphere</th>
<th>Peak</th>
<th>MNI coordinates</th>
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</table>

MNI, Montreal Neurological Institute; BSF, broad spatial frequency; HSF, high spatial frequency; LSF, low spatial frequency.
significant differences between groups were noted in the fMRI data, however. Of these, the most consistent finding was that of increased activation in the fusiform gyrus in both degraded conditions among the schizophrenia group in the baseline contrasts. At first glance, this seems to contradict studies indicating impaired face processing and reduced fusiform area activity in schizophrenia (Gur et al. 2002; Quintana et al. 2003; Fakra et al. 2008). However, these studies used paradigms that were either complex (e.g. involving simultaneous monitoring and evaluation of multiple stimuli) or involved affect processing, or otherwise resulted in very poor performance in the patient group, making it difficult to interpret the results (Yoon et al. 2006; Silverstein, 2008). More recent studies that have incorporated more appropriate control conditions (e.g. objects, as opposed to a blank stimulus field), and tasks that produced performance levels that are not confounded by generalized deficit issues (Knight & Silverstein, 2001), indicate that fusiform area activity is preserved in schizophrenia when processing faces (Yoon et al. 2006; Anilkumar et al. 2008). This then raises the possibility that increased fusiform activity may represent a compensatory mechanism by this intact area in the face of earlier processing impairments.

Evidence in support of the hypothesis of excessive neural activity during face processing when facial information deviates from what is typically present comes from several studies. For example, in a non-clinical study, Loffler et al. (2005) found that the fMRI blood oxygen level-dependent (BOLD) signal among populations of fusiform face area neurons increased during face processing as synthetically constructed faces deviated geometrically from a prototypical (mean) face. We propose that this is relevant to schizophrenia patients in the present study in that, because of earlier impairments in processing global information, the briefly presented information that is reaching the fusiform area is characterized by especially weakened form information, and thus represents a deviation from a prototypical face stimulus. This view is consistent with recent findings by Chen et al. (2008a) and Butler et al. (2008) indicating that schizophrenia patients require longer stimulus durations (increased signal strength) to processes faces normally. It is possible that what both the present findings and those of Chen et al. (2008a) and Butler et al. (2008) reflect is that form-deficient information is reaching the fusiform area, requiring a greater than normal degree of feature assembly or analysis before a face representation is formed. This hypothesis is consistent with our findings of increased left fusiform area activation in schizophrenia in the LSF condition, as opposed to the normal finding of increased right fusiform area activity during holistic face processing (Kanwisher, 2004; Maurer et al. 2007).

Also consistent with the hypothesis of increased fusiform area activation representing a compensatory mechanism in schizophrenia, Herrmann et al. (2006) found increased ERP amplitudes during emotionally neutral face processing in schizophrenia, especially among paranoid patients. Similarly, Leitman et al. (2008) found increased network activity during face processing in schizophrenia, which was interpreted as exaggerated efforts at integrating perceptual aspects of the face, the situation we hypothesize to be occurring secondary to earlier failures in perceptual organization. It is important to note that it is unlikely that the excessive activation was related to gender processing, given past studies demonstrating independence of fusiform face area activity and gender discrimination, and the role of this area in face stimulus processing but not categorization (Rossion et al. 1999).

There were some differences between the between-group comparisons on the baseline contrasts (e.g. HSF versus fixation) compared with the between-condition contrasts (e.g. HSF minus BSF). Notably, as discussed above, using the baseline contrasts, the schizophrenia group demonstrated increased activity in the fusiform gyrus in both the HSF and LSF conditions. With the between-condition contrasts, however, patients demonstrated significantly increased fusiform gyrus activity only in the LSF condition. As this was the condition where their behavioral performance was poorer than that of controls, and where it was predicted that patients would have the most difficulty (due to their perceptual organization impairment and the lack of feature-based information in this condition), compensatory fusiform gyrus activity might be especially expected here. Of interest, with this contrast, controls showed greater early visual cortex activity than patients, whereas patients were more active than controls in the fusiform gyrus. In the contrast between the HSF and BSF condition, however, patients did not demonstrate increased fusiform gyrus activity, but did demonstrate increased visual cortex activity. This may reflect their increased ability (compared to controls) to process features early in visual processing (Place & Gilmore, 1980), and perhaps less of a requirement for fusiform gyrus involvement in this condition, where patients were relatively more able (compared to LSF, and compared to controls) to assemble faces from the available information. In sum, the between-group data from the baseline and the between-condition contrasts support the idea that: (1) with low spatial frequency
information, controls engage in more early visual cortex activity, suggesting increased processing of global stimulus properties; (2) with high spatial frequency information, patients engage in more early visual cortex activity, suggesting increased early processing of individual features; and (3) with both HSF and especially LSF faces, patients demonstrate increased fusiform gyrus activation, perhaps as compensatory processing due to reduced quality of global information accumulated from earlier visual cortex regions. It should be noted here that, although, conceptually, the between-condition contrasts (which involve subtraction of BSF data) should provide more information about the spatial frequency manipulations than the baseline contrasts (which compare each condition to the fixation condition), these contrasts unfortunately have reduced signal-to-noise ratios, and increased variability because they involve voxel-wise subtraction. Therefore, in the discussion above, the results from both sets of contrasts are essentially weighted equally when interpreting the data.

Limitations of this study are the relatively small sample size and the gender differences between groups. We consider it unlikely that the observed group differences are secondary to gender, however, given that past findings of impairments in face processing, low spatial frequency processing or perceptual organization in schizophrenia cannot be accounted for by gender effects, and that no gender effects in the fusiform gyrus were found in a prior fMRI study of perceptual organization in schizophrenia (Silverstein et al. 2009). Nevertheless, past studies of basic, non-affective, face perception demonstrate that females are superior to males (McBain et al. 2009), and so further work is needed to determine the extent to which our observed results are due to a schizophrenia-related impairment, a gender effect, or an interaction of the two. Another potential limitation is that the use of a block design raises the possibility of order effects in the data. Replication of the present findings, with a larger and more gender-matched subject sample, using an event-related design would increase the strength of evidence for compensatory fusiform gyrus activity during face processing in schizophrenia, and help to clarify the extent to which the observed effects are due to the stimuli versus the context of their presentation. Finally, it should be noted that the face stimuli had hair visible, and therefore that in some cases male-female judgments may have been based on hair features as opposed to, or in addition to, facial features. This source of noise can be eliminated by showing only the face region in future studies.

For the schizophrenia group, medication dose was positively related to performance in the HSF, and to a lesser extent the BSF, conditions. Of interest, in the condition where patients were hypothesized to have the greatest difficulty (LSF), dose was unrelated to performance. These findings raise the possibilities that medication improves feature binding, or that higher medication doses characterize higher functioning patients. However, the former hypothesis is inconsistent with the lack of a significant correlation in the LSF condition, and with past findings that dopamine receptor blocking medication either has a negligible effect on early visual processing (Butler & Javitt, 2007) or is more likely to cause overactivity in low spatial frequency channels (Kéri et al. 2002), which characterized the LSF but not the HSF condition in this study. The latter hypothesis is inconsistent with the generally low levels of symptoms in the patient sample. An alternative hypothesis is that patients on higher doses of medication are more severely ill, and that this includes a visual integration impairment and its associated over-reliance on feature-based processing. This would account for the pattern of significant or trend-level correlations between medication dose and performance in only the conditions where high spatial frequency information was present (i.e. the HSF and BSF, but not LSF, conditions). It is also consistent with past findings that visual integration impairments are found in patients with a more severe form of illness characterized by poor pre-morbid functioning and greater behavioral and linguistic disorganization (Silverstein et al. 1996; Knight & Silverstein, 1998; Uhlhaas & Silverstein, 2005). However, more direct investigations of the relationships between pre-morbid functioning, symptoms, medication dose and behavioral and fMRI data from face processing tasks are necessary before confidence can be gained in the hypothesis that the observed data reflect the presence of an illness subtype, especially because the correlations were not significant when corrected for multiple analyses. Nevertheless, to the extent that face processing abnormalities in schizophrenia reflect, in part, reduced perceptual organization, which this study suggests is the case, it will be important to determine if abnormal face processing characterizes the same subgroup of patients that have consistently been shown to most strongly demonstrate perceptual organization impairments.

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Declaration of Interest

None.

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