A Reversal of the Normal Pattern of Parahippocampal Response to Neutral and Fearful Faces Is Associated with Reality Distortion in Schizophrenia

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Background: *Individuals with schizophrenia demonstrate impaired recognition of facial expressions and may misattribute emotional salience to otherwise nonsalient stimuli. The neural mechanisms underlying this deficit and the relationship with different symptoms remain poorly understood.*

Methods: *We used event-related functional magnetic resonance imaging to measure neural responses to neutral, mildly fearful, and prototypically fearful facial expressions. The sample included 15 medicated individuals with chronic schizophrenia (SZ) and 11 healthy control individuals (CON), matched for gender (all male), age, and years of education.*

Results: *A repeated measures 3 × 2 analysis of variance (ANOVA) revealed a significant interaction between expression intensity and group in right parahippocampal gyrus ($p < .01$). Individuals with chronic schizophrenia demonstrated a decrease, whereas CON showed an increase, in right parahippocampal gyrus response to increasingly fearful expressions. Between-group comparison revealed greater activation in SZ than CON in right parahippocampal gyrus to neutral faces. The reality distortion dimension, but not neuroleptic medication dose, was positively associated with the right parahippocampal gyral and right amygdalar response to neutral faces in SZ.*

Conclusions: *An abnormally increased parahippocampal response to neutral faces was positively associated with reality distortion in SZ. This may underlie the previously reported finding of a misattribution of emotional salience to nonsalient social stimuli in schizophrenia.*

Key Words: Schizophrenia, fMRI, facial expressions, dimensions

A characteristic feature of schizophrenia is impaired interpersonal function, with social/occupational dysfunction forming one of the diagnostic criteria of the disorder (American Psychiatric Association 1994). It has been postulated that impaired processing of facial expressions may underlie the social-communicative problems in individuals with the disorder, and numerous studies have demonstrated facial expression recognition deficits in schizophrenia (see reviews of Morrison et al 1988; Mandal et al 1998; Edwards et al 2002). According to some authors, the facial affect recognition deficit varies depending on the phase of illness (Mueser et al 1997) or psychopathological symptoms (Heimberg et al 1992; Schneider et al 1995), whereas others (Bellack et al 1996; Addington and Addington 1998) reported no effect of illness duration, symptoms, and medication levels on the performance. Studies directly addressing the issues of specificity of this deficit have compared performance of individuals with schizophrenia and those with affective disorders, demonstrating a greater overall impairment in schizophrenia, with no significant difference between subjects with affective disorders and control subjects (Feinberg et al 1986; Loughland et al 2002). It should also be noted, however, that some findings have indicated abnormal facial affect recognition in depression compared with healthy control subjects (Gur et al 1992; Surguladze et al 2004).

With regard to the emotion recognition deficit in schizophrenia, there have been reports indicating an emotion specificity of this deficit, particularly for negative facial expressions, e.g., for fear (Evangeli and Broks 2000), fear and disgust (Mandal and Rai 1987), or sadness (Silver et al 2002). Findings from studies employing visual scanpath measurements to examine visual attention to facial stimuli have further demonstrated an avoidance of salient facial features and a restricted visual scanning style for emotional faces in individuals with schizophrenia (Streit et al 1997; Loughland et al 2002). Other studies have demonstrated similar patterns of abnormal visual attention in deluded individuals with schizophrenia viewing neutral and threat-related visual material (Phillips and David 1997). Green et al (2003) found in paranoid individuals with schizophrenia a marked tendency to attend to less threatening facial expressions. These findings were interpreted as evidence of increased sensitivity to threat and subsequent threat avoidance in this population.

Neuroimaging studies have helped to delineate the neural systems involved in the processing of facial expressions, in particular those depicting fear, in healthy populations. While many of these studies have highlighted the role of the amygdala in the response to fearful expressions (Morris et al 1996; Whalen et al 1998), others have additionally implicated the hippocampus in the response to these expressions (Critchley et al 2000; Lange et al 2003; Williams et al 2001). In a recent study (Surguladze et al 2003), our group demonstrated linear trends of increasing activation in bilateral fusiform cortex, dorsomedial frontal gyrus, and right hippocampus in response to the increasing degrees of fearful facial stimuli (neutral, mild fear, prototypical fearful expression). Findings from neuroimaging studies in schizophrenic populations, however, indicate reduced or absent amygdalar and hippocampal responses to fearful facial expressions (Hempel et al 2003; Gur et al 2002),

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Received July 7, 2005; revised November 8, 2005; accepted November 23, 2005.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2005.11.021

associated in particular with paranoid symptoms (Phillips et al 1999; Williams et al 2004). These neuroimaging findings of reduced activity in neural systems underlying the normal response to threat are consistent with the above findings of fearful facial expression recognition deficits and the direction of visual attention away from threatening stimuli in individuals with schizophrenia.

One possibility is that the relative decreases in amygdalar and hippocampal responses to fearful expressions are secondary to reduced amygdalar and hippocampal volumes consistently found in structural neuroimaging studies in schizophrenic populations (Bogerts et al 1990; Niu et al 2004). Another possibility is that these regions demonstrate dysfunctional rather than decreased responses per se, such that abnormal *increases* in response occur to stimuli other than those depicting prototypical displays of fear, for example, neutral or more positive facial expressions. Indeed, in one previous study, a relative increase in amygdalar response to happy but not fearful expressions was demonstrated in individuals with schizophrenia (Kosaka et al 2002). In a recent positron-emission tomography (PET) study (Taylor et al 2002), in addition to a decreased amygdalar response in schizophrenic individuals, a positive correlation was demonstrated between the left amygdalar response and the severity of positive symptoms in these individuals to nonaversive pictures from the International Affective Picture System (Lang and Greenwald 1988).

These findings provide some evidence of impaired emotion, and particularly threat, processing in individuals with positive symptoms of schizophrenia. However, the relationships between abnormalities in emotion processing and specific categories of positive symptoms or negative symptoms in schizophrenia remain unclear. One way to examine these relationships is to employ a dimensional approach to the measurement of schizophrenic symptomatology (Liddle 1987b). Here, symptoms of schizophrenia are grouped into three separate syndromes of reality distortion, disorganization, and psychomotor poverty. Findings from a subsequent neuroimaging study using positron emission tomography (Liddle et al 1992) indicated that the three syndromes corresponded to distinguishable and coexisting neuropathological processes. In particular, reality distortion syndrome was positively associated with the regional cerebral blood flow (rCBF) in the left parahippocampal region, while the disorganization syndrome was negatively associated with rCBF in right ventral prefrontal cortex and the psychomotor poverty syndrome was negatively associated with rCBF in left dorsolateral prefrontal cortex. Understanding of the pathophysiologic processes underlying different symptoms of schizophrenia can therefore be furthered by the combination of functional neuroimaging techniques and employment of the dimensional approach to the measurement of symptom severity.

In this study, using an event-related functional magnetic resonance imaging (fMRI) design, we aimed to examine in individuals with schizophrenia:

1. Neural responses to prototypically fearful and other, nonprototypically fearful expressions, including neutral and mildly fearful expressions.
2. The relationship between specific symptom dimensions of the disorder and patterns of neural response to these stimuli.

Based on findings from previous studies, we hypothesized that schizophrenic individuals compared with healthy control individuals would show decreased amygdalar and hippocampal responses to prototypically fearful expressions. We were also able to hypothesize that the magnitude of amygdalar and hippocampal responses would be positively correlated with the severity of persecutory-themed positive symptoms, in particular the reality distortion symptom dimension, in schizophrenic individuals.

Methods and Materials

Participants

Fifteen male individuals with a DSM-IV diagnosis of schizophrenia were recruited from outpatient clinics of the South London and Maudsley Trust, United Kingdom. The diagnosis of schizophrenia was made by psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (First et al 1995). Eleven healthy male control individuals matched for age and years of education were recruited from ancillary staff at the Maudsley Hospital and the local population. Exclusion criteria for all participants were illicit substance or alcohol abuse at least 2 years prior to participation in the study. No participant had serious traumatic brain injury leading to loss of consciousness or structural brain lesions, the latter determined by a radiologist at the time of neuroimaging. All participants were right-handed (Oldfield 1971). An estimate of premorbid intelligence quotient (IQ), the National Adult Reading Test (NART) (Nelson 1982), indicated significantly higher scores in control subjects [$t(24) = -4.2$; $p < .001$]. Participants also completed the Beck Depression Inventory (BDI) (Beck et al 1986); schizophrenic patients were significantly more depressed than control subjects [$t(24) = 2.31$; $p < .05$].

To determine the severity of negative and positive symptoms, individuals with schizophrenia were assessed on the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983) and the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen 1984) (Table 1). These ratings were performed by two independent raters. Interclass correlations for SAPS and SANS were alpha = .98 and .95, respectively.

Ratings for the severity of each of the three symptom dimensions in schizophrenia, reality distortion, psychomotor poverty, and disorganization, were derived from the SANS and SAPS scores for each individual with schizophrenia as described previously (Liddle 1987a). The reality distortion syndrome included the following symptoms: auditory hallucinations directed to the patient, delusions of persecution, and delusions of reference. The disorganization syndrome included inappropriate

Table 1. Participant Characteristics

	Patients ($n = 15$)	Control Subjects ($n = 11$)
Mean Age (SD)	43.1 (8.8)	36.8 (10.6)
Years of Education	12.1 (2.3)	13.5 (3.6)
NART-IQ[b]	110.8 (8.6)	122.2 (3.0)
BDI[a]	15.3 (14.3)	4.9 (6.3)
SANS	27.9 (14.6)	
SAPS	25.1 (23.9)	
Mean Reality Distortion (Range)	3.7 (0–9)	
Mean Disorganization (Range)	1.5 (0–6)	
Mean Psychomotor Poverty (Range)	3.3 (0–9)	

NART, National Adult Reading Test; IQ, intelligence quotient; BDI, Beck Depression Inventory; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

[a] $p < .05$.

[b] $p < .001$.

affect, poverty of content of speech, and positive formal thought disorder. The psychomotor poverty syndrome included blunt affect, poverty of speech, and decreased spontaneous movement.

Illness duration in individuals with schizophrenia ranged from 3 to 30 years, with a mean of 19.9 (SD = 10.5) and mean number of prior hospitalizations 5.7 (SD = 5.4); all were taking atypical antipsychotic medications, including risperidone, olanzapine, and clozapine. Medication doses had been optimized by the attending psychiatrists. While there are no completely satisfactory dose equivalents for the newer antipsychotics, there are guidelines for chlorpromazine equivalents of clozapine (American Psychiatric Association 1977) and equivalents for the other newer antipsychotics (Woods 2003), which allow a valid approximation to be made. Using these approximations, the chlorpromazine equivalent dose range was 100 mg to 1200 mg per day, and mean dose equivalent was 487.1 mg per day.

All participants gave informed consent and ethical approval was obtained from the Ethical Committee of the South London and Maudsley Trust and Institute of Psychiatry.

Neuroimaging Task

Study subjects participated in one 6-minute experiment employing event-related fMRI, where they were presented with 10 different facial identities, each identity expressing 50% and 100% intensities of fear, in addition to a neutral expression (Facial Expressions of Emotion: Stimuli and Tests) (Young et al 2002). There were thus 30 different facial stimuli in total; each stimulus was presented twice for 2 seconds. Individuals therefore viewed 60 stimuli in total. The order of facial identities and expression type was randomized such that there was no successive presentation of the same identity or facial expression type. During the interstimulus interval, the duration of which was varied from 3 seconds to 8 seconds according to a Poisson distribution with an average interval of 5.9 seconds, individuals viewed a fixation cross. They were requested to decide on the gender of face stimuli and press one of two buttons accordingly. Subjects were familiarized with the task procedure before the scanning.

Acquisition

Gradient-echo echoplanar imaging (EPI) data were acquired on a GE Signa 1.5 T system (General Electric, Milwaukee, Wisconsin) at the Maudsley Hospital, London. A quadrature birdcage head coil was used for radiofrequency (RF) transmission and reception. A total of 180 T2*-weighted images depicting blood oxygenation-level dependent (BOLD) contrast (Ogawa et al 1992) were acquired over 6.02 minutes at each of 16 near-axial noncontiguous 7-mm thick planes parallel to the intercommissural (anterior commissure-posterior commissure [AC-PC]) line: echo time (TE) 40 milliseconds, repetition time (TR) 2 seconds, inplane resolution 3.44 mm, interslice gap .7 mm. In the same scanning session, an inversion recovery EPI dataset was acquired at 43 near-axial 3-mm thick planes parallel to the AC-PC line: TE 73 milliseconds, inversion time (TI) 180 milliseconds, TR 16 seconds, inplane resolution 1.72 mm, interslice gap .3 mm. This higher resolution EPI dataset provided whole brain coverage and was later used to register the fMRI datasets acquired from each individual in standard stereotactic space.

Analysis of Neuroimaging Data

Individual Brain Activation Maps. Data were analyzed with software developed at the London Institute of Psychiatry, using a nonparametric approach. Data were first processed (Bullmore et al 1999a) to minimize motion-related artefacts. Following realignment, data were then smoothed using a Gaussian filter (full-width at half maximum [FWHM] 7.2 mm) to improve the signal-to-noise characteristics of the images.

Responses to the experimental paradigms were then detected by first convolving each component of the experimental design with each of two gamma variate functions (peak responses at 4 and 8 seconds, respectively). The best fit between the weighted sum of these convolutions and the time series at each voxel was computed using the constrained BOLD effect model suggested by Friman et al (2003). This reduces the possibility of the model-fitting procedure giving rise to mathematically plausible but physiologically implausible results. Following computation of the model fit, a goodness of fit statistic was computed. This consisted of the ratio of the sum of squares of deviations from the mean image intensity (over the whole time series) due to the model to the sum of squares of deviations due to the residuals (sum of squares [SSQ] ratio). This statistic is used to overcome the problem inherent in the use of the F (variance ratio) statistic that the residual degrees of freedom are often unknown in fMRI time series due to the presence of colored noise in the signal. Following computation of the observed SSQ ratio at each voxel, the data were permuted by the wavelet-based method described and extensively characterized in Bullmore et al (2001). Repeated application of this method at each voxel followed by recomputation of the SSQ ratio from the permuted data allows (by combination of results over all intracerebral voxels) the data-driven calculation of the null distribution of SSQ ratios under the assumption of no experimentally determined response. Using this distribution, it is possible to calculate the critical value of SSQ ratio needed to threshold the maps at any desired type I error rate. The detection of activated voxels was extended from voxel to cluster level using the method described in detail by Bullmore et al (1999b). In addition to the SSQ ratio, the size of the BOLD response to each experimental condition was computed for each individual at each voxel as a percentage of the mean resting image.

To calculate the BOLD effect size, the difference between the maximum and minimum values of the fitted model for each condition was expressed as a percentage of the mean image intensity level over the whole time series.

Group Maps. The observed and permuted SSQ ratio maps for each individual, as well as the BOLD effect size maps, were transformed into standard space (Talairach and Tournoux 1988) using the two-stage warping procedure described in detail elsewhere (Brammer et al 1997). Cluster level maps are thresholded at < 1 expected type I error cluster per brain.

Group Comparisons. Comparisons of responses between groups or experimental conditions was performed by fitting the data at each intraceberal voxel at which all subjects have nonzero data using a linear model of the type

$$Y = a + bX + e$$

where Y is the vector of BOLD effect sizes for each individual, X is the contrast matrix for the particular intercondition/group contrasts required, a is the mean effect across all individuals in the various conditions/groups, b is the computed group/condition difference, and e is a vector of residual errors. The model is fitted by minimizing the sum of absolute deviations rather than the sum of squares to reduce outlier effects. The null distribution of b is computed by permuting data between conditions/groups (assuming the null hypothesis of no effect of experimental condition or group membership) and refitting the above model.

Group difference maps were computed as described above at voxel or cluster level by appropriate thresholding of the null distribution of b.

Voxelwize and clusterwise between-group differences in BOLD signal change to the three different types of facial expression versus baseline were then examined using a 3 × 2 repeated measures analysis of variance (ANOVA), with intensity (neutral, 50% fear, 100% fear) as the within-subject variable and group (individuals with schizophrenia, control subjects) as the between-group variable. This analysis therefore allowed for the examination of any main effect or interaction between group and expression intensity, using whole-brain statistical maps. Between-group differences were further explored using values of BOLD signal change extracted from any cluster uncovered by the whole-brain ANOVA.

Results

The 3 × 2 ANOVA of the whole brain statistical data produced a difference map [interaction intensity by group; $F(1.4,34.3) = 3.8$; $p < .05$] comprising one cluster centered within the right parahippocampal gyrus, which extended into the right hippocampus (coordinates: x = 18/22, y = −18/−22, z = −18/−23). There were no other main effects or interactions. The significant interaction was driven by the greater BOLD response in the right parahippocampal gyrus to neutral faces in individuals with schizophrenia compared with control subjects (Mann-Whitney $U = 40.0$, $p < .05$).

This interaction indicated that while control subjects showed an increased BOLD signal change to increasing intensity of fearful facial expression (neutral–mild–intense fear), the opposite pattern of a decrease in BOLD signal was demonstrated by individuals with schizophrenia (Figures 1 and 2).

Subsequent whole-brain post hoc tests comparing individuals with schizophrenia and control subjects with regard to processing of each of the facial stimulus versus baseline contrasts (neutral, mild fear, prototypical fear versus baseline fixation cross) demonstrated a significant between-group difference to the neutral condition only. In addition to an increased response within the right parahippocampal gyrus to neutral faces, individuals with schizophrenia also demonstrated significantly increased (compared with control subjects) BOLD signal change in three additional clusters: left parahippocampal and bilateral fusiform gyri (Figures 3 and 4; Table 2). In these regions, individuals with schizophrenia demonstrated decreased responses to mild and intensely fearful expressions, while control subjects demonstrated opposite, although nonsignificantly different, patterns of responses.

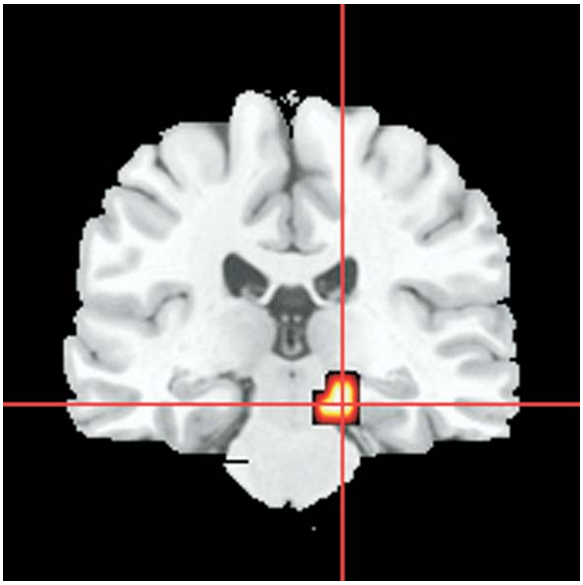

Figure 1. Interaction between intensity and group. Coronal view of the brain demonstrating the cluster with significantly different trends in responses to facial expressions of increasing intensity of fear: the activation in right parahippocampal gyrus (x = 18, y = −22, z = −18) was decreasing in individuals with schizophrenia and increasing in control subjects. The right and the left sides of the brain slice are displayed on the right and left sides of the image, respectively.

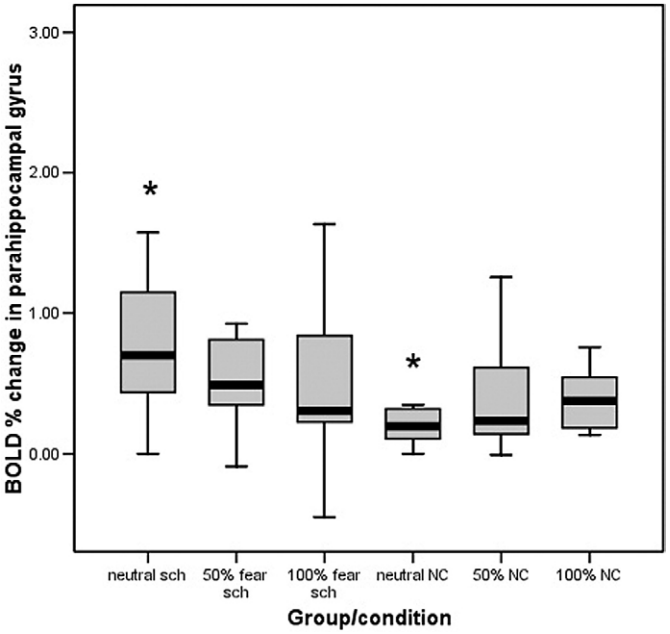

Figure 2. BOLD percent changes in parahippocampal gyrus during processing of faces with different expressions. Boxplots represent the magnitude of BOLD signal change in the cluster in the parahippocampal gyrus where the interaction between intensity and group was demonstrated. Y-axis: BOLD percent change; X-axis indicates conditions by group: neutral sch – individuals with schizophrenia processing neutral faces; 50% fear sch – individuals with schizophrenia processing faces with 50% intensity of fear; 100% fear sch – individuals with schizophrenia processing faces with 100% intensity of fear; neutral NC, 50% NC, and 100% NC – control subjects processing neutral faces, 50% fearful faces, and 100% fearful faces, respectively. *BOLD response in schizophrenia > control subjects, Mann-Whitney $U = 40.0$; $p < .05$. BOLD, blood oxygenation level-dependent.

The Relationship Between Symptom Dimensions and Right Parahippocampal Response

Correlational analyses revealed a significant positive correlation between the reality distortion syndrome score and mean BOLD signal change in the right parahippocampal gyrus to neutral (Spearman's rho = .74; $p < .01$) and to mildly fearful faces (Spearman's rho = .52; $p < .05$). No significant correlations were demonstrated between either the disorganization or psychomotor poverty syndrome and BOLD signal change within this region to any of the three facial expression types.

After covarying for BDI score, only the positive correlation between the reality distortion syndrome score and the BOLD signal change in the right parahippocampal gyrus for the response to neutral expressions remained significant: $r(df, 12) =$

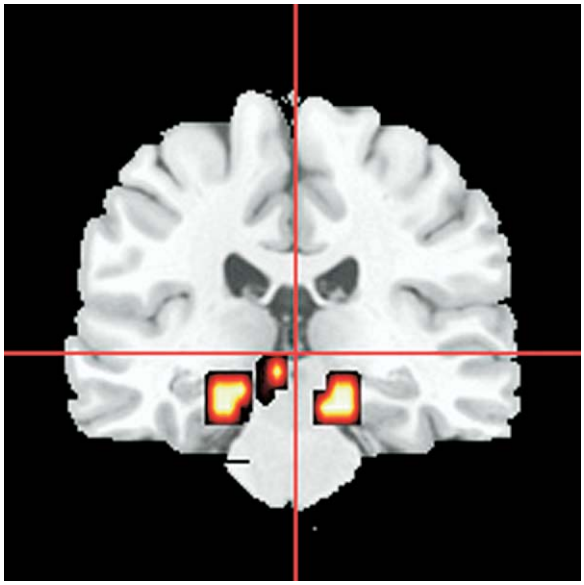

Figure 3. Between-group differences in neural responses to neutral faces: bilateral parahippocampal gyri. Coronal view of the brain where the individuals with schizophrenia demonstrated significantly greater than control subjects responses to neutral faces within bilateral parahippocampal gyri (coordinates: x = 18, y = −22, z = −23; x = −18, y = −22, z = −18). The right and the left sides of the brain slice are displayed on the right and left sides of the image, respectively.

.57, p = .03. This correlation also remained significant after controlling for IQ: $r(df, 12)$ = .56, p = .04.

To examine further any potential association between BDI score, IQ score, and right parahippocampal gyral response to neutral expressions in individuals with schizophrenia, we performed additional correlational analyses. These analyses did not reveal any significant correlations bewteen either BDI score or IQ score and magnitude of BOLD signal change within right parahippocampal gyrus to neutral expression in individuals with schizophrenia.

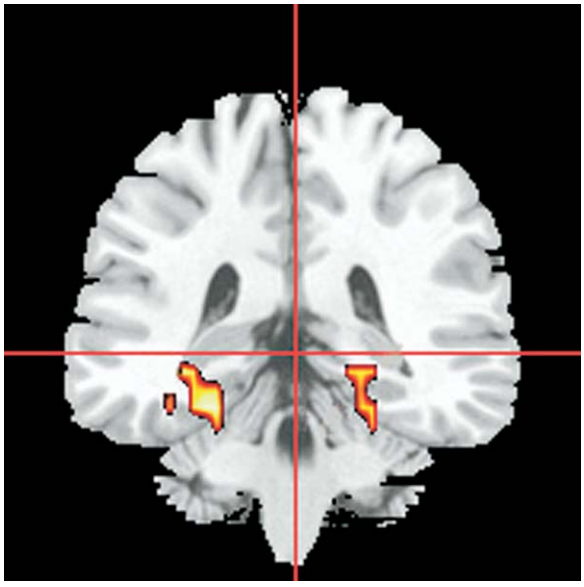

Figure 4. Between-group differences in neural responses to neutral faces: bilateral fusiform cortex. Coronal view of the brain where the individuals with schizophrenia demonstrated significantly greater than control subjects responses to neutral faces within bilateral fusiform cortex (coordinates: x = 36, y = −37, z = −13; x = −32, y = −37, z = −13). The right and the left sides of the brain slice are displayed on the right and left sides of the image, respectively.

Table 2. Clusters in Which Individuals with Schizophrenia Demonstrated Significantly Greater Responses than Control Subjects to Neutral Faces

Location (Broadmann Area)	Talairach Coordinates x	y	z	Mann-Whitney *U*	*p*-Value
L Fusiform Gyrus (37)	−32	−37	−13	36	.016
L Parahippocampal Gyrus (35)	−18	−22	−18	44	.046
R Parahippocampal Gyrus (35)[a]	18	−22	−23	40	.027
R Fusiform Gyrus (37)	36	−37	−13	29	.005

L, left; R, right.
[a]The cluster involved in the interaction of group by intensity.

To clarify the effect of specific symptoms on the activation in right parahippocampal gyrus, the values representing the reality distortion as well as hallucinations and delusions scores were entered into a linear stepwise regression. The only significant association was demonstrated between BOLD signal change to neutral faces and the reality distortion score: B =.079 (SE = .027); β =.63; p = .013, explaining 39% of variance. Separately taken scores of hallucinations or delusions did not significantly contribute to the model.

The Amygdalar Response

The 3 × 2 whole-brain ANOVA did not reveal a differential activation in either of the amygdalae between individuals with schizophrenia and control subjects. To explore the nature of potential association of amygdalar response with the psychopathological dimensions, the mean values of percent change in BOLD signal were extracted from regions centered within the right and left amygdalae (coordinates: x = +/−24; y = −6, z = −13) to all three types of facial expression versus baseline. Correlational analyses were then performed between these values and scores of the three syndromes: reality distortion, disorganization, and psychomotor poverty. There was a significant positive correlation between BOLD signal change in the right amygdala to neutral faces only and reality distortion scores: Spearman's rho = .55; p = .03. There was no significant association between BOLD signal change in either of the amygdalae and scores of the other symptom dimensions to neutral faces.

Further exploratory analyses revealed that to 100% fearful faces, the right amygdalar and right parahippocampal BOLD signal changes correlated significantly in the schizophrenia group (Pearson r = .66; p = .007; Spearman's rho = .53; p = .04) (Figure 5).

Behavioral Data

To examine any between-group differences in reaction time during performance of the gender decision task in the scanner, a repeated measures 3 × 2 ANOVA with intensity (neutral, 50%, 100%) as the within-subject variable and group (individuals with schizophrenia, control subjects) as the between-subject factor was performed. This did not reveal any significant main effects of intensity or group, or interactions, on reaction time. The proce-

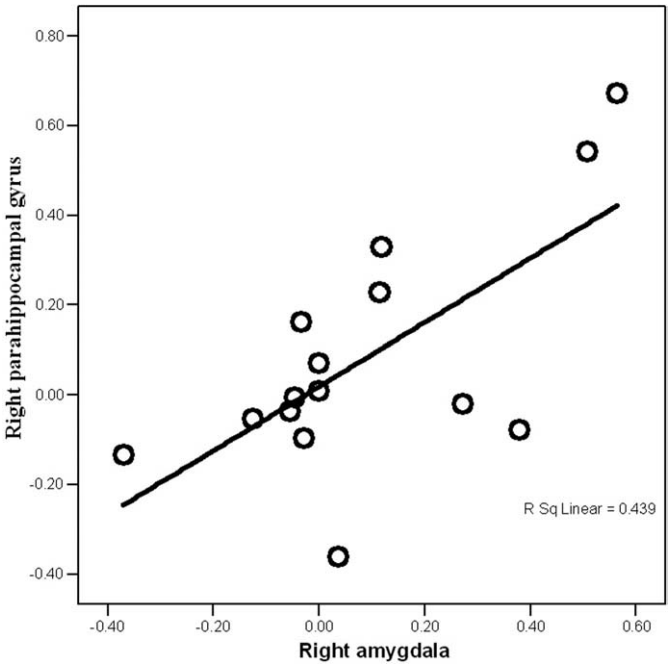

Figure 5. Correlation between right amygdalar and right parahippocampal response to 100% fearful faces in individuals with schizophrenia: Pearson $r = .66$; $p = .007$; Spearman's rho = .53; $p = .04$. X-axis: BOLD percent change in right amygdala; Y-axis: BOLD percent change in right parahippocampal gyrus.

dure was repeated for performance accuracy. This did not show any main effects or interaction.

Effect of Medication

To estimate the possible effects of medication, the values of BOLD signal change within the right parahippocampal gyrus and right amygdala for each of the facial expression-baseline contrasts were correlated with medication dose in chlorpromazine equivalents. There were no significant correlations between the medication dose and the above BOLD response values.

Discussion

We aimed to examine neural responses to fearful and neutral facial expressions in individuals with schizophrenia and the relationship between specific symptom dimensions and patterns of neural response to these stimuli in this population. Our findings demonstrate for the first time that individuals with schizophrenia can be distinguished from healthy control subjects by their differential patterns of neural response to fearful and neutral faces. While individuals with schizophrenia demonstrated a negative trend in magnitude of response in the right parahippocampal gyrus to expressions of increasing intensities of fear, i.e., greater response to neutral than mild or intense fear, control subjects demonstrated a positive trend in this response, i.e., increased response to intense versus mild fear and neutral face. The significant interaction between group and intensity within the right parahippocampal gyrus was determined by the greater response to neutral faces in this region in individuals with schizophrenia compared with control subjects. Regression analysis confirmed the positive association between right parahippocampal gyral response to neutral faces and reality distortion but no other symptom dimension scores in individuals with schizophrenia.

While these findings do not support our hypothesis of a decrease in amygdalar and hippocampal response to prototypically fearful expressions, they do indicate a positive association between the reality distortion dimension and abnormal neural responses to facial expressions in individuals with schizophrenia. The center of the abnormal response was within the right parahippocampal gyrus rather than the hippocampus or amygdala, although it extended into the right hippocampus. Further analyses did reveal a positive association between right amygdalar response to neutral faces and reality distortion in these individuals.

As part of the limbic system, the parahippocampal gyrus has multiple, direct connections with the hippocampus and amygdala, however, and is involved in novelty detection (Schroeder et al 2004), episodic and spatial memory (Tsikiura et al 2002; Malkova and Mishkin 2003), and context appraisal (Sacchetti et al 1999). A dysfunctional parahippocampal gyrus could therefore be associated with impaired context appraisal and associative learning, resulting in errors in validation of external sensory inputs (Prasad et al 2004). Neuroimaging studies (Silbersweig et al 1995; (Epstein et al 1999; Shergill et al 2000) have provided further data supporting an association between increased response within hippocampus and parahippocampal gyrus (among other brain structures) and positive symptoms of schizophrenia. In the present study, the involvement of the right parahippocampal gyrus in emotion processing was additionally suggested by the observed positive association between the right amygdala and right parahippocampal gyrus responses to intense fear expressions in individuals with schizophrenia.

An association between an abnormally increased parahippocampal gyral response to neutral faces and the reality distortion symptom dimension also supports clinical observations in individuals with schizophrenia with prominent persecutory symptoms of perception of threat in nonthreatening or inappropriate contexts. Findings from studies measuring visual attention to pictures of social scenes have demonstrated in schizophrenic individuals with persecutory delusions increased visual attention to neutral but not to overly threatening components of these scenes (Phillips et al 2000) and a direction of attention away from the facial features of fearful expressions (Green et al 2003). The observed positive association between the reality distortion dimension and amygdalar activity to neutral faces is also consistent with previous findings in individuals with schizophrenia of a correlation between positive symptoms and amygdalar response to predominantly nonaversive rather than aversive stimuli (Taylor et al 2002) and a misattribution of negative emotion labels to neutral faces (Kohler et al 2003). Together, these findings suggest that the reality distortion dimension of schizophrenia may be associated with an increased perception of threat from inappropriate stimuli, such as those classified as neutral by healthy individuals.

Other authors (Liddle 1987a; Liddle et al 1992) have postulated an involvement of the left rather than right hippocampus and parahippocampal gyrus in the psychopathology of schizophrenia, based on clinical neuropsychological findings or those from studies measuring resting blood flow. We found abnormally increased responses in individuals with schizophrenia in both left and right parahippocampal gyri to neutral faces, although the significant positive correlation between neural responses to neutral faces and realty distortion was found only within the right parahippocampal gyrus. This lateralization may relate to the right hemisphere involvement in face processing per se (Kolb et al 1983). Responses in the left parahippocampal gyrus and bilateral fusiform gyri showed the same, although nonsignificant, trends

as those in the right parahippocampal gyrus: BOLD signal changes in all these areas were greatest to neutral rather than to mild or intensely fearful faces. The control subjects in our study demonstrated the opposite trend of response: greater BOLD signal changes in the right parahippocampal gyrus to intense than to mild fear or neutral expressions. These latter data are a replication of our previous findings of increased response in right parahippocampal gyrus in healthy individuals to facial expressions of increasing intensity of fear (Surguladze et al 2003).

Our findings highlight the importance of adopting a syndrome dimension approach to the examination of neural responses in schizophrenic populations. In previous studies, it has often proved difficult and somewhat artificial to categorize individuals with schizophrenia into different subgroups on the basis of the presence or absence of different types of positive or negative symptoms, in view of the presence in these individuals of differing numbers and severity of symptoms (Phillips et al 1999). In the present study, we were able to measure the relationship between specific syndrome dimensions and neural responses within one group of individuals with schizophrenia without the above artificial subdivision. It is noteworthy that only the reality distortion syndrome showed a strong association with the BOLD signal change in the right parahippocampal gyrus: none of the separate symptom scores (paranoid delusions or hallucinations) explained this association. We therefore suggest that the reality distortion syndrome represents a valuable composite measure of paranoid psychotic states with a specific neural substrate.

The issue of depression as a possible confounder deserves a special consideration, as some studies have shown that depression may be associated with an impaired recognition of facial affect (Gur et al 1992; Surguladze et al 2004) and is an important comorbid clinical feature of schizophrenia (Hafner et al 2005), which may correlate with the positive symptoms (Baynes et al 2000). We therefore examined the extent to which the abnormal increase in right parahippocampal gyral response to neutral faces in individuals with schizophrenia reflected reality distortion rather than the low mood observed in these individuals. The positive association between the reality distortion score with the BOLD signal change in the right parahippocampal gyrus to neutral faces remained after controlling for depression score. Furthermore, there was no significant correlation between the depression severity and magnitude of the right parahippocampal gyral responses to neutral facial expressions in individuals with schizophrenia. It is additionally unlikely that our findings can be explained in terms of between-group differences in IQ, as the above analyses failed to reveal any significant effect of IQ on right parahippocampal response to neutral faces in individuals with schizophrenia.

There was no correlation between antipsychotic medication dosage in chlorpromazine equivalents and BOLD signal change. Our patients were treated with risperidone, olanzapine, and clozapine. All of these medications produce high occupancy levels of serotonin $(5\text{-HT})_{2A}$ receptors at clinically effective doses (Travis et al 1998; Kapur et al 2000). Thus, the level of occupancy across all of the patients is likely to be very similar and therefore binding, as this receptor subtype is unlikely to have accounted for any effects seen on clinical dimensions or BOLD signal change. The method we used to calculate chlorpromazine equivalents is based primarily on effective clinical dose equivalents. Although this is likely to reflect binding at a variety of receptors, the most robust correlation between average antipsychotic dose used to treat schizophrenia and receptor affinity is for the dopamine D_2 receptor (Creese et al 1976). It is therefore likely that any medication effect in this study would be driven by binding of the medications to this receptor. As we found no correlation between medication dose equivalents and BOLD signal changes, it is unlikely that our findings can be explained by differences in dopamine D_2 receptor occupancy or availability.

It is possible that direction of visual attention and scanning away from the fearful expressions in the schizophrenic population accounted for the between-group differences in neural response in paralimbic and visual areas. There were no between-group differences, however, in reaction time during performance of the online facial attentional task (gender decision) to any of the stimuli, again suggesting that the individuals with schizophrenia were processing all facial stimuli. The face gender discrimination task requires limited attentional resources (Reddy et al 2004). Therefore, even in the case of attending away from the fearful faces, individuals with schizophrenia should have been able to efficiently perform the task. Indeed, the robust level of BOLD response in visual cortical areas found in individuals with schizophrenia suggested that they were processing all facial stimuli, including fearful faces. We acknowledge, however, that the best control for between-group differences in viewing strategies for facial expressions would be the simultaneous recording of visual scanpaths and this should be a focus of future research.

A limitation of this study is that the sample included male participants only, which makes it less generalizable to the female population. The exclusion of female participants in this study allowed the exclusion of any potential effect of gender on the lateralization of neural responses to emotional stimuli (e.g., Cahill et al 2001). Additionally, the schizophrenic group included many chronic patients, which prevents the generalization of our findings to all individuals with schizophrenia. On the other hand, inclusion of chronic patients made it possible to examine the role of a broader psychopathology (e.g., psychomotor poverty and disorganization syndromes) in modulation of neural responses. Importantly, the only syndrome associated with the abnormal neural response was that of reality distortion.

In summary, our findings are the first to demonstrate an increased response within the parahippocampal and fusiform gyri to neutral faces, as well as a decrease in right parahippocampal response to mild and intensely fearful faces in individuals with schizophrenia, the opposite pattern to that observed in control subjects. Additionally, there was a positive association between the realty distortion dimension and magnitude of response in the right parahippocampal gyrus and right amygdala to neutral faces in individuals with schizophrenia. We suggest that these findings may reflect an abnormally increased perception of neutral faces as potentially more salient and threatening in individuals with schizophrenia with the reality distortion, consistent with clinical observations of threat perception in inappropriate contexts in this population. Future studies employing longitudinal designs in high-risk populations can further elucidate the extent to which this pattern of abnormal neural responses reflects a cause or effect of the disorder.

Dr. K. Kucharska-Pietura was supported by the Wellcome Trust International Research Fellowship award.

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