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Neuronal Correlates of Facial Emotion Discrimination in Early Onset Schizophrenia

Nina Y Seiferth*[,1], Katharina Pauly[1], Thilo Kellermann[1], N Jon Shah[2,3,4], Gudrun Ott[5], Beate Herpertz-Dahlmann[6], Tilo Kircher[1], Frank Schneider[1,3] and Ute Habel[1]

[1]Department of Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany; [2]Institute of Neuroscience and Biophysics—Medicine, Research Center Jülich, Jülich, Germany; [3]Brain Imaging Center West, Jülich, Germany; [4]Institute of Physics, University of Dortmund, Dortmund, Germany; [5]Department of Child and Adolescent Psychiatry and Psychotherapy, University of Düsseldorf, Düsseldorf, Germany; [6]Department of Child and Adolescent Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany

Emotion discrimination deficits represent a well-established finding in schizophrenia. Although imaging studies addressed the cerebral dysfunctions underlying emotion perception in adult patients, the question of trait *vs* state characteristics is still unresolved. The investigation of juvenile patients offers the advantage of studying schizophrenia at an age where influences of illness course and long-term medication are minimized. This may enable a more detailed characterization of emotion discrimination impairments and their cerebral correlates with respect to their appearance and exact nature. A total of 12 juvenile patients with early onset schizophrenia and matched healthy juveniles participated in this study. fMRI data were acquired during an emotion discrimination task consisting of standardized photographs of faces displaying happy, sad, angry, fearful, or neutral facial expression. Similar to findings in adult patients, juvenile patients exhibited reduced performance specificity whereas sensitivity was unaffected. Independent of the valence, their processing of emotional faces was associated with hypoactivations in both fusiform gyri and in the left inferior occipital gyrus. In addition, hyperactivations in patients were found in the right cuneus common to happy, angry, and fearful faces. Further, most distinct changes were present in juvenile patients when processing sad faces. These results point to a dysfunction in cerebral circuits relevant for emotion processing already prominent in adolescent schizophrenia patients. Regions affected by a decrease in activation are related to visual and face processing, similar to deficits reported in adult patients. These changes are accompanied by hyperactivations in areas related to emotion regulation and attribution, possibly reflecting compensatory mechanisms.
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INTRODUCTION

Affective disturbances, like parathymia or flattened affect, are key features of the psychopathology in schizophrenia. As the reliable perception and expression of emotions are essential for adequate social interaction and momentous to subjective well-being, emotion disturbances in schizophrenia have severe consequences for social functioning and the functional outcome of patients (Kee *et al*, 2003). Thus, the investigation of emotion dysfunctions is an important goal in schizophrenia research. Aspects of emotion processing addressed in this context include the perception and expression of one's own emotions and the discrimination of other people's emotions in mimic, gesture, or speech. Accordingly, several studies have demonstrated that deficits in recognizing, assessing, and experiencing emotions are part of the neuropsychological deficit profile of schizophrenia patients (Schneider *et al*, 1995).

Focusing on facial emotion perception many studies could show deficits in the processing of emotional facial expressions in schizophrenia patients (Feinberg *et al*, 1986; Heimberg *et al*, 1992; Kohler *et al*, 2003; Mueser *et al*, 1997; Penn *et al*, 2000; Schneider *et al*, 1995, 2006). A more detailed inspection of these impairments revealed that although the sensitivity to detect a specific emotion was preserved, the specificity was affected, ie schizophrenia patients exhibited problems in rejecting faces with other than the target emotional expression (Schneider *et al*, 2006). Furthermore, deficits in emotion processing correlate with the severity of psychotic symptoms (Kohler *et al*, 2000; Schneider *et al*, 1995). At the same time, they are relatively stable over the course of disease (Addington and Addington, 1998; Kohler *et al*, 2003) and were reported to be already present in subjects at risk for psychosis (Habel *et al*, 2004; Kee *et al*, 2004; Seiferth *et al*, 2008; van't Wout *et al*, 2004). Difficulties in emotion recognition may further be

*Correspondence: NY Seiferth, Department of Psychiatry and Psychotherapy, RWTH Aachen University, Pauwelsstrasse 30, Aachen D-52074, Germany, Tel: +49 241 80 89850, Fax: 49 241 8082 401, E-mail: nseiferth@ukaachen.de
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related to deficits in theory of mind and empathy (Langdon *et al*, 2006; Lee *et al*, 2004; Shamay-Tsoory *et al*, 2007). Therefore, they seem to reflect basal pathological mechanisms of the disorder.

An increasing number of imaging studies dealt with the neural correlates underlying emotion processing in schizophrenia. Structural imaging studies predominantly reported volume changes in regions relevant to emotion processing, such as the amygdala, the insula, the thalamus, and the hippocampus (Wright *et al*, 2000). Functional neuroimaging studies have demonstrated activation changes in the amygdala, the hippocampus, the prefrontal and cingulate cortices, and the occipital gyri in response to emotional stimuli in patients (Gur *et al*, 2002a; Hempel *et al*, 2003; Holt *et al*, 2006; Quintana *et al*, 2003; Russell *et al*, 2007; Schneider *et al*, 1998; Takahashi *et al*, 2004; Taylor *et al*, 2002; for a review see Aleman and Kahn, 2005). Besides the regularly reported hypoactivations in relevant brain regions, hyperactivations in temporal (hippocampus, amygdala) and frontal regions (Hempel *et al*, 2003; Holt *et al*, 2006; Kosaka *et al*, 2002; Russell *et al*, 2007) have also been observed. These changes are interpreted as compensation for dysfunctions in the underlying neural network.

Owing to the fact that emotion dysfunctions have been reported to be present before illness onset, there is reason to hypothesize that impairments in emotion processing do not result from illness chronification and long-term neuroleptic medication and are therefore also observable in early onset psychosis. Furthermore, emotion dysfunctions associated with poor social outcome (Kee *et al*, 2003) might have even stronger effects in patients with an early onset of illness, because those might interfere with the juveniles' social–emotional development. This is in line with evidence that childhood or adolescence onset predicts a more severe course of illness (Lay *et al*, 2000; Rapoport *et al*, 2005).

In healthy humans, the recognition of facial emotions develops continuously throughout childhood and adolescence, which is reflected by behavioral as well as neurobiological evidence (Herba and Phillips, 2004). It is assumed that the ability to recognize facial emotions is in part due to a biological readiness, but environmental factors are of importance as well (de Haan *et al*, 2004; Herba and Phillips, 2004). However, little is known about the influence of psychiatric disorders during childhood or adolescence on the development of this function. In preceding behavioral studies we demonstrated deficits in identifying a person's emotional state in children and adolescents with schizophrenia and other nonaffective psychoses (Habel *et al*, 2006), but the associated cerebral changes have not been addressed so far.

The present study was intended to characterize emotional dysfunctions and its neural correlates in early onset schizophrenia by applying an fMRI facial emotion discrimination paradigm. We hypothesized to find performance differences in emotion discrimination between juvenile schizophrenia patients and healthy juveniles. Further, we intended to describe the pattern of cerebral dysfunctions in brain areas related to emotion and face processing that have previously been reported to be affected in schizophrenia patients, such as structures in the limbic system, the prefrontal cortex, the anterior cingulate gyrus, and the fusiform gyrus. Neurobiological changes in early onset psychosis similar to those found in adult patients would underline an early appearance of emotion dysfunctions in the course of disease, independent of factors like long-term medication and illness chronification. On the other hand, there might be neurobiological changes specific to psychosis with an early onset and therefore pointing to risk factors during brain development.

PATIENTS AND METHODS

Subjects

A total of 12 male patients with early onset schizophrenia (<19 years of age) were recruited from the Departments of Child and Adolescent Psychiatry and Psychotherapy of the Universities of Aachen and Düsseldorf, Germany. Further, 12 healthy juveniles were recruited by means of local advertisements, followed by a detailed screening. They were matched pairwise to the patients according to gender (all male), age (mean ± 1.5 years), and years of parental education (mean ± 3 years). As expected, comparison of these socio-demographical variables revealed no significant group differences (Table 1).

Besides the usual exclusion criteria for MRI (eg metal implants), additional exclusion criteria for participation were psychiatric or neurological comorbidities, current substance abuse (amphetamine, benzodiazepine, cannabis, cocaine and opiates; verified by an urinal drug screening), other disorders affecting cerebral metabolism, impaired vision, or prosopagnosia (Benton Facial Recognition Test (BFRT)—Short Form; Benton *et al*, 1994). All participants were right-handed (Edinburgh Handedness Inventory, cut-off: $x \geqslant 8$; Oldfield, 1971).

Early onset schizophrenia patients were diagnosed by experienced child and adolescent psychiatrists following a comprehensive evaluation including psychiatric examination, record review, and clinical interviews (Structured Clinical Interview for DSM-IV, Wittchen *et al*, 1997; Kiddie-Sads—Present and Lifetime Version, Delmo *et al*, 2001). Furthermore, all participants were clinically assessed using the Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987), the Global Assessment Scale (GAS; Spitzer *et al*, 1976), and the Hamilton Depression Scale (HAMD, 21-item version; Hamilton, 1960). With regard to psychopathology, schizophrenia patients showed low to moderate psychotic and depressive symptoms. Further, they exhibited lower global functioning than healthy juveniles (Table 1).

The juvenile schizophrenia patients were on low doses of antipsychotic medication (compound for each subject, mg per day: clozapine 350; risperidone 6; clozapine 300; clozapine 150; risperidone 6; risperidone 4 + chlorprothixene 110; oxcarbazepine 300 + olanzapine 5; risperidone 5; clozapine 300; aripiprazole 20; clozapine 250 + aripiprazole 15; amisulpride 100 + promethazine 25). One patient additionally received antidepressants and sedatives if required (mirtazapine 45 + lorazepam 4). Mean dosage of medication in chlorpromazine equivalents was 231 ± 111 mg per day. Median duration of illness (time since the first clinical admission) was 38 weeks (min/max: 4/109).

A battery of neuropsychological measures was administered, testing attention and working memory (Continuous Performance Test—Identical Pairs, CPT, Weintraub and

Table 1 Group Means (M ± SD) and Group Comparisons (Two-Tailed *t*-Tests) for Socio-demographical, Neuropsychological, and Psychopathological Measures in Juvenile Schizophrenia Patients (Left) and Healthy Juveniles (Right)

	Juvenile patients	Healthy juveniles	Group comparisons
Age (years)	17.8 ± 1.4	17.9 ± 1.5	$t(11) = 0.26$, $p = 0.80$
Mean parental education (years)	10.1 ± 3.8	10.8 ± 3.4	$t(11) = 1.10$, $p = 0.30$
Verbal intelligence (MWT-B, IQ)	94.4 ± 10.7	94.9 ± 6.6	$t(22) = 0.16$, $p = 0.87$
Attention (CPT verbal—hits, %)	62.8 ± 30.4	63.4 ± 22.2	$t(22) = 0.06$, $p = 0.96$
Attention (CPT spatial—hits, %)	59.9 ± 25.1	66.5 ± 23.2	$t(22) = 0.67$, $p = 0.51$
Working Memory (BZT—hits, %)	53.8 ± 17.0	70.5 ± 11.3	$t(22) = 2.83$, $p = 0.01$
Processing speed (TMT-A, s)	32.9 ± 11.23	24.0 ± 6.1	$t(22) = -2.40$, $p = 0.03$
Cognitive flexibility (TMT-B, s)	90.3 ± 45.3	57.9 ± 22.2	$t(22) = -2.22$, $p = 0.04$
Cognitive flexibility (verbal fluency, sum)	29.5 ± 18.1	32.0 ± 12.0	$t(22) = 0.40$, $p = 0.69$
Facial recognition (BFRT—hits, %)	86.6 ± 5.7	84.0 ± 4.4	$t(22) = -1.27$, $p = 0.22$
Face memory (PFMT—hits, %)	69.6 ± 11.3	75.4 ± 8.5	$t(22) = 1.43$, $p = 0.17$
Face memory (PFMT delayed—hits, %)	68.5 ± 9.4	73.1 ± 11.1	$t(22) = 1.09$, $p = 0.29$
Emotion discrimination (PERT—hits, %)	75.8 ± 11.7	80.4 ± 8.1	$t(22) = 1.11$, $p = 0.28$
Global psychopathology (PANSS, global)	56.3 ± 22.2	30.9 ± 1.6	$t(20) = -3.61$, $p = 0.006$
Positive symptoms (PANSS, positive)	16.2 ± 8.1	7.2 ± 0.6	$t(20) = -3.50$, $p = 0.007$
Negative symptoms (PANSS, negative)	13.3 ± 6.9	7.2 ± 0.6	$t(20) = -2.80$, $p = 0.02$
Depressive symptoms (HAMD, sum)	6.5 ± 5.4	0.3 ± 0.5	$t(20) = -3.65$, $p = 0.005$
Global functioning (GAS, sum)	57.0 ± 15.8	86.7 ± 5.4	$t(20) = 5.66$, $p < 0.001$

Abbreviations: MWT-B, Multiple-Choice Vocabulary Intelligence Test—Version B; CPT, Continuous Performance Test—identical pairs; BZT, German Version of the Letter Digit Test; TMT-A/B, Trail Making Test—version A and B; BFRT, Benton Facial Recognition Test—Short Form; PFMT, Penn Face Memory Test; PERT, Penn Emotion Recognition Test; PANSS, Positive and Negative Syndrome Scale; HAMD, Hamilton Depression Scale; GAS, Global Assessment Scale.

Mesulam, 1985; German Version of the Letter Digit Test, BZT, Gold *et al*, 1997), executive functions (Verbal Fluency Test, Daum *et al*, 1996; Trail Making Test—version A and B, TMT-A/B, Reitan, 1958), premorbid verbal IQ (German Multiple-Choice Vocabulary Intelligence Test—version B, MWT-B, Lehrl, 1989) and face processing (Penn Face Memory Test, PFMT, Gur *et al*, 1993; Penn Emotion Recognition Test, PERT 40, Kohler *et al*, 2004; BFRT—Short Form, Benton *et al*, 1994). Juvenile patients and healthy juveniles differed significantly in the BZT, TMT-A, and TMT-B. No other considerable group differences regarding the measured cognitive and emotional functions were found (Table 1).

Permission for the study was obtained from the local ethics committee. After complete description of the study, written informed consent was obtained from all participants and their parents.

Stimuli

To examine emotion discrimination ability we used a modified version of the Facial Emotions for Brain Activation (FEBA) test (Gur *et al*, 2002b; Schneider *et al*, 2006), presented by Presentation 0.70 software (Neurobehavioral Systems Inc., San Francisco, USA). Stimuli consisted of colored photographs of faces—balanced with regard to age, sex, and ethnicity—showing different emotional facial expressions (happy, sad, angry, fearful) or no emotion (neutral). The development and evaluation of the FEBA task has been reported in detail elsewhere (Gur *et al*, 2002b) and this paradigm has already been successfully used in previous behavioral (Schneider *et al*, 2006) and neuroimaging studies (Gur *et al*, 2002a; Seiferth *et al*, 2008).

Task

The event-related fMRI paradigm consisted of four randomly presented runs in which the participants had to decide whether the displayed pictures showed a specific target emotion (happiness, sadness, anger, fear) or any other emotion/no emotion. Each run consisted of 120 faces (32 targets, 32 nontargets, and 56 neutral). Every stimulus was presented for 2 s with an interstimulus interval of 1 s (blank screen) and randomly inserted null events (blank screen; 1.5–4.5 s). Participants responded by pressing a button on an fMRI-compatible response system (LUMItouch; Lightwave Technologies, Richmond, Canada) with their left or right index finger.

Finally, an age discrimination task, a face recognition task, and an emotion–cognition interaction paradigm were also administered, which are not reported here.

Data Acquisition

Structural and functional imaging was performed on a 1.5 T Sonata MR scanner (Siemens Medical Systems, Erlangen, Germany) located in the Research Center Jülich. Structural images were acquired by means of a three-dimensional T1-weighted MP-RAGE sequence (voxel size: $1 \times 1 \times 1\,mm^3$, sagittal FoV: $256 \times 256\,mm^2$, 160 slices, TR = 2.2 s, TE = 4 ms, TI = 1200 ms, $\alpha = 15^\circ$). Functional data were collected with EPI sensitive to BOLD contrast (T2*, voxel size: $3.125 \times 3.125 \times 3\,mm^3$, 64×64 matrix, FoV: $200 \times 200\,mm^2$,

30 slices, whole brain, ascending, 3 mm slice thickness, gap = 0.3 mm, TR = 3 s, $\alpha = 90^{\circ}$). Owing to subcortical susceptibility-induced signal loss (Deichmann *et al*, 2002) an EPI sequence with variable echo time (40–60 ms) was applied, providing optimized BOLD sensitivity (Stöcker *et al*, 2006).

Analysis of non-fMRI data was accomplished by means of SPSS, version 14 (SPSS Inc., Chicago, IL, USA). Error probability was predefined at $p < 0.05$ (two tailed). If Levene's test for equality of variances revealed significance, corrections of the degrees of freedom as well as the *p*-values (Greenhouse–Geisser) were undertaken. Emotion discrimination performance was assessed by sensitivity (true positives/(true positives + false negatives)), specificity (true negatives/(true negatives + false positives)), and reaction time (RT; for both hits and correct rejections). Repeated-measures ANOVAs with the within-subject factor 'emotion' (happy, sad, angry, fearful) and the between-subject factor 'group' (juvenile patients, healthy juveniles) were performed. *Post hoc* analyses of significant effects were performed by *t*-tests (Bonferroni corrected for multiple comparisons). Owing to technical problems, performance data (fear condition) of one participant were not recorded and could hence not be included. Socio-demographical data (matching criteria) were compared by paired *t*-tests, neuropsychological and psychopathological measures by two-sample *t*-tests. fMRI data analysis was accomplished by SPM2 software (Wellcome Department of Cognitive Neurology, London, UK). Corrections for differences in signal intensity due to the applied variable TE, slice time correction, realignment, co-registration, stereotaxic normalization ($2 \times 2 \times 2\,mm^3$), an 8 mm FWHM Gaussian smoothing kernel and a high-pass filter (<7.81 mHz), were applied.

For single-subject statistics the different event types (happy, sad, angry, fearful, and neutral faces) were defined as regressors. Realignment parameters (*x*, *y*, *z*, pitch, roll, and yaw) and 'percent signal change'—an index of data variability and quality control (Stöcker *et al*, 2005)—were added as covariates. The resulting intrasubject contrast images entered random effects group analysis by means of repeated-measures ANOVA (mixed design) with the within-subject factor 'emotion' and the between-subject factor 'group'. Contrasts were defined for each emotional condition *vs* implicit baseline (blank screen) and *vs* neutral faces and analyzed for both groups separately as well as for group comparisons. Significance level was set to $p < 0.05$, FWE corrected (extent threshold: $k > 5$ voxels).

To define group differences in brain activation related to emotion processing independent of the specific emotion quality, conjunction analysis ($p < 0.05$, FWE corrected) was performed over the four within-emotion contrasts of group comparisons.

Correlation analyses (Pearson's correlation, two-tailed, $\alpha = 0.05$) were performed between emotion discrimination performance (sensitivity, specificity, and RTs) and parameter estimates of the significant voxels from the conjunction analysis. Further, behavioral performance was correlated with neuropsychological measures, patients' psychopathology, and medication.

Brain structure labeling was performed using the Anatomical Automatic Labeling (Tzourio-Mazoyer *et al*, 2002) toolbox for SPM2.

RESULTS

Emotion Discrimination Performance

Analysis of sensitivity revealed a significant main effect for the factor 'emotion' ($F = 15.44$, d.f. = 3, 63; $p < 0.001$). No main effect of 'group' or an interaction 'emotion × group' was observed. *Post hoc* analysis demonstrated significant differences in sensitivity for the following pairwise comparisons: happy *vs* sad ($t = 2.97$, d.f. = 23, $p = 0.007$), happy *vs* angry ($t = 5.77$, d.f. = 23, $p < 0.001$), happy *vs* fearful ($t = 6.73$, d.f. = 22, $p < 0.001$), and sad *vs* fearful faces ($t = 4.31$, d.f. = 22, $p < 0.001$). In summary, participants exhibited highest sensitivity to happy and lowest to angry faces (Figure 1).

A different pattern resulted for analysis of specificity. Main effects for the factors 'emotion' ($F = 22.82$, d.f. = 3, 63; $p < 0.001$) and 'group' ($F = 5.95$, d.f. = 1, 21; $p = 0.02$) as well as a significant interaction 'emotion × group' ($F = 3.06$, d.f. = 3, 63; $p = 0.03$) were observed (Figure 1).

Fragmenting the main effect 'emotion' by *post hoc* analyses revealed significant differences for happy *vs* sad ($t = 7.89$, d.f. = 23, $p < 0.001$), happy *vs* angry ($t = 3.54$, d.f. = 23, $p = 0.002$), happy *vs* fearful ($t = 4.29$, d.f. = 22, $p < 0.001$), sad *vs* angry ($t = -4.35$, d.f. = 23, $p < 0.001$), and sad *vs* fearful faces ($t = -3.46$, d.f. = 22, $p = 0.002$). Thus, participant exhibited highest specificity to happy and lowest to sad faces. As reflected in the main effect 'group', patients revealed lower overall specificity. Finally, *post hoc* analysis of the interaction 'emotion × group' revealed no significant differences, but a trend toward worse specificity in patients when discriminating sad ($\alpha = 0.013$ Bonferroni corrected; $t = 2.45$, d.f. = 11, $p = 0.03$) and angry faces ($t = 2.74$, d.f. = 11, $p = 0.02$).

Analysis of RTs revealed a significant main effect of 'emotion' with regard to RT hits ($F = 19.28$, d.f. = 3, 63; $p < 0.001$) and RT correct rejections ($F = 22.80$, d.f. = 3, 63; $p < 0.001$), as well as a significant interaction 'emotion × group' for RT hits ($F = 4.34$, d.f. = 3, 63; $p = 0.008$), but no further significant effects (Figure 2).

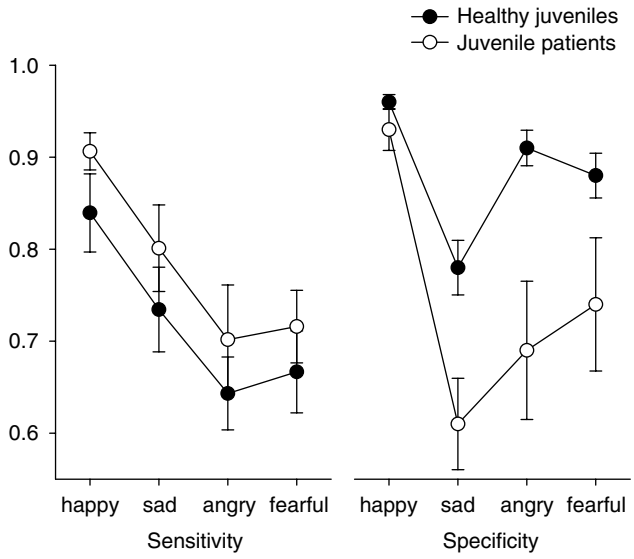

Figure 1 Emotion discrimination performance (M ± SE) ie sensitivity (left) and specificity (right) for healthy juveniles and juvenile schizophrenia patients. There was no significant group difference for sensitivity, but for specificity.

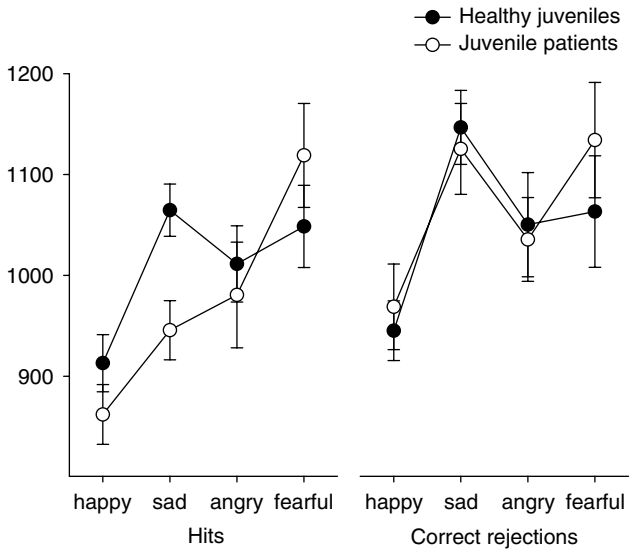

Figure 2 Reaction times (M ± SE) for hits (left) and correct rejections (right) in emotion discrimination for healthy juveniles and juvenile schizophrenia patients.

Post hoc analyses of RT for hits revealed the following significant pairs: happy *vs* sad ($t=-5.23$, d.f. $=23$, $p<0.001$), happy *vs* angry ($t=-4.80$, d.f. $=23$, $p<0.001$), happy *vs* fearful ($t=-7.23$, d.f. $=22$, $p<0.001$), and angry *vs* fearful faces ($t=-3.08$, d.f. $=22$, $p=0.005$). Analyses of RT for correct rejections showed differences for happy *vs* sad ($t=-6.97$, d.f. $=23$, $p<0.001$), happy *vs* angry ($t=-3.25$, d.f. $=23$, $p=0.004$), happy *vs* fearful ($t=-6.20$, d.f. $=22$, $p=0.001$), and sad *vs* angry faces ($t=1.84$, d.f. $=23$, $p=0.002$), respectively. Thus, subjects always reacted fastest on happy and slowest on fearful faces (RT hits) or sad faces (RT correct rejections). Finally, *post hoc* analysis of the interaction 'emotion × group' for RT hits revealed that patients reacted significantly faster than healthy juveniles when identifying a sad face ($t=3.04$, d.f. $=22$, $p=0.006$).

To exclude that group differences in emotion discrimination performance were due to global neuropsychological differences, the patients' psychopathological symptoms or medication (in chlorpromazine equivalents), correlation analyses were performed. As expected, a significant positive correlation emerged between the emotion discrimination performance (sensitivity) measured by the FEBA test (inside the scanner) and by the PERT test (outside the scanner) for both patients ($r=0.60$, $p=0.04$) and healthy subjects ($r=0.59$, $p<0.05$). In addition, healthy subjects showed a negative correlation between RTs for hits and face recognition ability measured by the BFRT. In patients, specificity ($r=0.74$, $p=0.009$) and the corresponding RTs ($r=-0.61$, $p=0.04$) correlated with face recognition ability in the BFRT, as well as specificity values correlated with face memory capacity (PFMT; $r=0.61$, $p<0.05$). No other significant correlations were observed.

Changes in Brain Activity Underlying Face Processing and Emotion Discrimination in Juvenile Patients

Neural activation patterns underlying emotion discrimination in juvenile schizophrenia patients were directly compared to those of healthy juvenile subjects. Analysis revealed hypoactivations in the inferior occipital gyrus (happy, sad, and angry faces), the fusiform gyrus (happy, angry, and fearful faces), the thalamus (happy, sad, and angry faces), and the superior temporal gyrus (sad and fearful faces). Further, hypoactivations associated with the processing of sad faces were observed in patients in the middle and superior occipital gyri, in hippocampal regions, in the posterior cingulate gyrus and inferior parietal regions, in the insula and the cerebellum. On the other hand, juvenile schizophrenia patients exhibited hyperactivations in the cuneus/calcarine sulcus (happy, angry, fearful faces), the precuneus and inferior frontal gyrus (angry faces; Table 2; Figure 3).

Further characterizing these group differences independent of the emotional valence, conjunction analyses for group contrasts of the different emotions were performed. Analyses revealed that a hypoactivation in patients in the fusiform gyrus bilaterally and in the left inferior occipital gyrus was common to all emotions (maxima at $x=-36$, $y=-70$, $z=-10$, $k_E=187$, $T_{Max}=7.48$, $P_{FWE}<0.05$, and $x=32$, $y=-78$, $z=-6$, $k_E=168$, $T_{Max}=6.61$, $P_{FWE}<0.05$). Further, a hyperactivation of the right cuneus (maximum at $x=8$, $y=-82$, $z=14$, $k_E=31$, $T_{Max}=5.25$, $P_{FWE}<0.05$) emerged in patients in comparison to controls when performing a conjunction over happy, angry, and fearful faces (sad faces were left out due to missing group differences in this contrast).

Correlation of Brain Activation and Behavioral Performance

Correlation analysis of parameter estimates extracted from the significant regions in the conjunction analysis (left inferior occipital gyrus (−36, −70, −10), right fusiform gyrus (32, −78, −6), right cuneus (8, −82, 14)) with behavioral performance (sensitivity, specificity, and RTs over all emotions) revealed a significant negative correlation of sensitivity with the activation related to neutral faces ($r=-0.60$, $p=0.04$) in the right fusiform gyrus (32, −78, −6) in patients, whereas there was no corresponding correlation in control subjects. Further, no other significant correlations between sensitivity/specificity and the parameter estimates in these three brain regions were observed for patients or controls. Thus, an increased overall sensitivity is related to less activation in the fusiform gyrus on neutral faces in patients but not in control subjects.

RT values correlated positively with the processing of faces in the fusiform gyrus (RT hits—happy: $r=0.63$, $p=0.03$; sad: $r=0.59$, $p<0.05$; RT correct rejections—happy: $r=0.75$, $p=0.005$; sad: $r=0.64$, $p=0.02$; angry: $r=0.60$, $p=0.04$; fearful: $r=0.63$, $p=0.03$; neutral: $r=0.70$, $p=0.01$) and the inferior occipital gyrus (RT correct rejections—happy: $r=0.59$, $p=0.04$) in control subjects, whereas there were no significant correlations of RTs and parameter estimates in patients (Figure 4). Further, there were no significant correlations between behavioral performance and parameter estimates in the cuneus.

Thus, a strong activation of the fusiform/inferior occipital gyri was related to higher RTs, whereas there was no such relation in patients.

Table 2 Facial Emotion Discrimination (SPM2, Repeated-Measures ANOVA, $p<0.05$ FWE Corrected, $k>5$ Voxels, MNI Coordinates, k_E = cluster size): Contrasts of Emotional Faces > Baseline for the Group Comparisons Healthy Juveniles > Juvenile Patients (Top) and Juvenile Patients > Healthy Juveniles (Bottom)

Region	Side	*x*	*y*	*Z*	k_E	T_{Max}
Healthy juveniles > Juvenile patients						
Happy						
Inferior occipital gyrus	R	−36	−70	−10	192	7.49
Fusiform gyrus	L	32	−78	−6	185	6.61
Thalamus	—	0	−16	2	6	4.90
Sad						
Inferior occipital gyrus	R	−34	−72	−8	3361	10.82
Parahippocampal gyrus	R	−2	−22	−18	99	7.12
Caudate	R	−14	−14	22	87	5.97
Superior temporal gyrus	L	60	−44	20	107	5.77
Posterior cingulum	—	0	−36	24	45	5.64
Thalamus	L	16	−34	16	59	5.35
Middle occipital gyrus	L	48	−78	18	33	5.30
Superior occipital gyrus	L	22	−80	30	38	5.29
Middle temporal gyrus	L	44	−62	14	29	5.26
Rolandic operculum	L	60	−20	16	26	5.18
Hippocampus	L	40	−8	−14	7	5.15
Insula	L	30	−18	20	79	5.09
Cerebellum	R	−16	−40	−20	33	5.01
Superior temporal gyrus	R	−38	−38	12	14	5.00
Middle temporal gyrus	L	66	−22	−4	15	4.96
Cerebellum	L	20	−36	−20	8	4.92
Gyrus supramarginalis	L	62	−48	40	11	4.86
Inferior parietal cortex	L	50	−24	−6	6	4.77
Angry						
Inferior occipital gyrus	L	−36	−70	−10	406	8.82
Fusiform gyrus	R	32	−78	−6	380	8.03
Thalamus	L	−2	−18	2	29	5.41
Fearful						
Fusiform gyrus	L	−26	−78	−8	517	8.46
Fusiform gyrus	R	32	−78	−8	285	8.04
Superior temporal gyrus	R	46	−38	6	6	4.81
Juvenile patients > healthy juveniles						
Happy						
Cuneus	R	8	−82	18	198	6.72
Sad						
—	—	—	—	—	—	—
Angry						
Cuneus	R	8	−82	18	283	7.44
Precuneus	L	−4	−54	8	58	5.62
Precentral/inferior frontal gyrus	L	−56	10	32	7	5.18
Cuneus	L	−8	−66	22	12	4.97
Fearful						
Calcarine sulcus/cuneus	R	8	−82	14	31	5.25

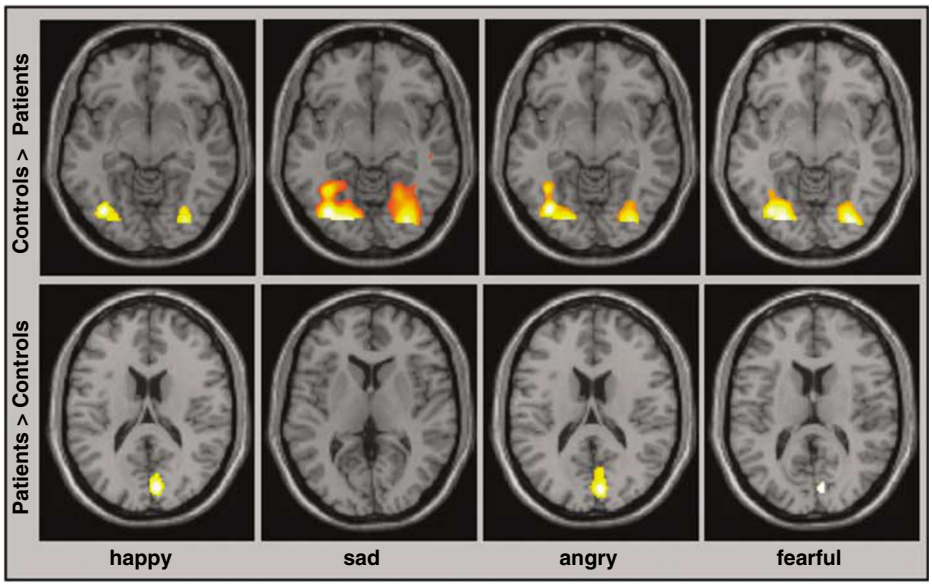

Figure 3 Main activation clusters (SPM2, repeated-measures ANOVA, $p<0.05$, FWE corrected) for the group contrast healthy juveniles > juvenile patients (top) and juvenile patients > healthy juveniles (bottom) for the processing of faces showing happy, sad, angry, and fearful expressions (conjunction analysis).

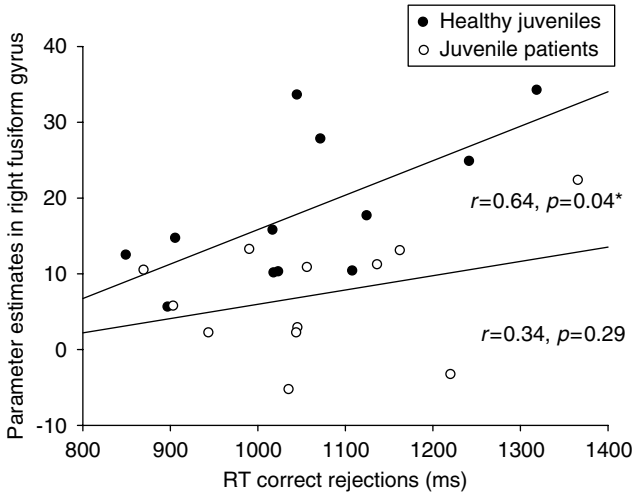

Figure 4 Correlation analysis of mean parameter estimates in the right fusiform gyrus at 32, −78, −6 when discriminating sad faces with mean reaction times for correct rejections. A significant positive correlation was present in healthy juveniles ($r=0.64$, $p=0.04$) but not in juvenile patients ($r=0.34$, $p=0.29$).

Correlation analysis of parameter estimates in the above-mentioned areas with medication (in chlorpromazine equivalents) as well as with depressive symptoms (sum score on the HAMD; Table 1) revealed no significant correlations.

DISCUSSION

Impaired Specificity in Emotion Discrimination in Patients

Analysis revealed a consistent influence of emotional valence on performance. In detail, the participants were most accurate regarding both sensitivity and specificity when discriminating happy faces whereas the sensitivity to angry as well as the specificity in discriminating sad faces exhibited the least performance. Accordingly, all subjects reacted fastest to happy faces and slowest reactions were observed on sad and fearful faces.

In addition, although no group differences were found for emotion discrimination sensitivity, juvenile patients showed lower overall performance than control subjects regarding specificity. Despite a nonsignificant *post hoc* analysis of the significant interaction, a trend toward a worse specificity in patients was observed when discriminating sad and angry faces. Finally, juvenile patients reacted significantly faster on sad faces than healthy juveniles.

Correlation analysis between emotion discrimination performance and neuropsychological as well as psychopathological measures could underline that the observed group differences in emotion discrimination performance were not due to global differences in neuropsychological ability or the patients' psychopathological symptoms. Further, emotion discrimination performance during fMRI measurement was comparable to the performance outside the scanner for both patients and healthy juveniles. Finally, face recognition ability as well as memory for faces might have contributed to specificity deficits in emotion discrimination in the patients, although no overall group differences in face recognition performance or face memory were observed.

In summary, although the ability to reject nonhappy faces was comparable for healthy juveniles and juvenile patients, specificity for sad, angry, and fearful faces was worse in patients. These results are in keeping with former studies on emotion discrimination ability in schizophrenia that reported similar impairments in correct rejections while sensitivity to detect the target emotion was preserved (Schneider *et al*, 2006).

Decreased Activation during Facial Emotion Processing in Juvenile Patients

Several functional imaging studies reported that brain regions in the visual cortex exhibit stronger activation to emotional faces than to neutral faces, including face-selective areas in the fusiform gyrus (Critchley *et al*, 2000;

Ishai *et al*, 2004; Surguladze *et al*, 2003; Vuilleumier *et al*, 2001; Winston *et al*, 2003). Further, cerebral regions such as the amygdala, insula, hippocampal regions, striatum, cingulate cortex as well as prefrontal areas are involved in the processing of emotion perception (Phillips *et al*, 2003). Structural abnormalities as well as a failure to activate such regions sufficiently have been demonstrated for adult schizophrenia patients (Wright *et al*, 2000). In line with the literature on adult patients, the present study in juveniles was able to show decreased activation in response to faces with different emotional content in areas associated with visual and face processing such as the occipital gyri, fusiform gyri, the insula and regions in the limbic system, namely the thalamus, the hippocampus, and the cingulate cortex. In sad faces, the superior temporal gyrus, inferior parietal regions, and the cerebellum additionally were less activated in patients. The observed decrease in activity associated with the processing of different emotional facial expressions in patients was further underlined by significant hypoactivations of the fusiform gyri and the left inferior occipital gyrus that was independent of the specific emotion. Further, the activations found in the fusiform gyrus were not correlated with RT performance in patients, although there was a correlation in healthy juveniles. Thus, processing depth was associated with a decrease in processing speed in healthy juveniles but not in patients. Further, patients' sensitivity showed a negative correlation to fusiform activation on neutral faces, which was not observable in controls, underlining the importance of a changed processing of neutral faces in the course of schizophrenia, as it was recently reported for risk subjects (Seiferth *et al*, 2008).

Our results indicate that patients with early onset schizophrenia exhibit neurobiological changes in brain areas associated with face and emotion processing similar to those found in adult patients as well as a decoupling of discrimination performance and activation of the fusiform gyrus. These data do not support the assumption that deficits in processing of faces and their emotional content develop during and/or are a result of illness chronification and long-term medication. Further, the results are in line with evidence showing decreased activation of the fusiform gyrus associated with impaired face processing and social cognition in nonclinical samples, as subjects at risk for psychosis (Seiferth *et al*, 2008), and in other clinical samples with related behavioral impairments, such as autism patients (Schultz *et al*, 2003).

In particular, the processing of sad faces seems to be altered in juvenile patients. Our data revealed the most extensive hypoactivations when discriminating sad faces were observed in several regions relevant to face and emotion processing including the thalamus, the occipital gyri, the insula, the hippocampus, the posterior cingulate gyrus, and inferior parietal cortex. This underlines the role of negative emotion processing in schizophrenia as found in previous studies examining adult schizophrenia patients (Habel *et al*, 2004; Schneider *et al*, 1998).

Upregulation of Brain Activity as Compensatory Processes?

In contrast to the observed hypoactivations, several hyperactivations were observed in the juvenile patients, in detail in the cuneus/calcarine sulcus, the precuneus, and the inferior frontal gyrus. These hyperactivations were common to all facial expressions except sadness. All these regions are known to be involved in the regulation of emotions, especially the inferior frontal gyrus, and in empathic judgment as well as the attribution of emotions to the self or other people, in this case predominantly the precuneus (Cavanna and Trimble, 2006). Therefore, increased activities in these regions might be understood as compensatory processes, which are able to attenuate but not counterbalance deficits completely. Previous functional imaging studies have demonstrated such compensatory brain activation in schizophrenia patients regarding cognitive functions, such as working memory (Tan *et al*, 2006).

The assumption of a regulatory or compensatory mechanism in the juvenile patients is in line with the observation that the adolescent patients were not impaired in identifying the target emotion during the discrimination task, but in the rejection of nontarget faces. Moreover, the patients were most impaired in specificity when discriminating sad faces and, in addition, they reacted significantly faster than healthy juveniles when identifying sad faces as such. Thus, a possible compensatory mechanism based on an increase in cuneus, precuneus, and inferior frontal activation might be lacking when processing sad faces, given the observation that no hyperactivations were associated with the discrimination of sad faces. This might result in the described performance deficits, particularly with regard to specificity. These results are supported by previous studies describing specific performance deficits for negative emotions in children and adolescents with schizophrenia and other psychoses (Habel *et al*, 2006) as well as impairments in processing sadness on a neural level in adult schizophrenia patients (Habel *et al*, 2004; Schneider *et al*, 1998).

Furthermore, previous findings on the brain activation changes underlying the development of emotion processing have to be taken into account when interpreting these results. Recent studies could document developmental differences in the degree to which engagement of affective circuitry contributes to emotion recognition. Juveniles show a higher level of amygdala activity than adults as well as increased activity in the fusiform gyrus when viewing emotional faces (Hare *et al*, 2008; Guyer *et al*, 2008), whereas adults show an increased participation of frontal regions (Gunning-Dixon *et al*, 2003). As an early onset of schizophrenia is related to a poor prognosis (Lay *et al*, 2000; Rapoport *et al*, 2005) it has to be clarified how these regular changes in emotion processing during development interact with the dysfunctional changes underlying the development of illness.

Limitations and Conclusions

Some limitations of the present findings have to be taken into account. First, sample size was relatively small. Nevertheless, we found a statistically significant effect even with correction for multiple comparisons. Thus, effects in our sample are quite robust and large. Further, only male juveniles were included in this study. This has to be taken into account when generalizing our results to a female population. But the overall rather homogeneous sample of

this study has the advantage of less possible confounding factors or heterogeneity regarding differences in gender, age, age of illness onset, illness duration, chronicity, and previous treatments.

Finally, an influence of medication on the results has to be considered, as the patients received neuroleptic drugs in moderate dosage. There is little reason to expect a specific effect of medication on emotion processing in early onset schizophrenia as deficits in facial emotion processing in adult schizophrenia patients were demonstrated to be present independent of neuroleptic medication (Kohler *et al*, 2003). Further, brain areas known to be affected by such agents to date are the basal ganglia and the frontal cortex (Lane *et al*, 2004). Further, we found no relevant correlations between activity in the reported brain regions and medication. Thus, it is not likely that such an effect of medication is accounting for the reported results.

In conclusion, this study indicates that early onset schizophrenia patients exhibit slight deficits in emotion discrimination performance with regard to the rejection of nontargets. Further, the patients exhibited decreased activation in brain areas related to face and emotion processing. On the other hand, these juvenile schizophrenia patients showed differences in brain activation in the sense of hyperactivations in frontal as well as parietooccipital regions as the precuneus and the cuneus, which might reflect compensatory processes in these areas. Regarding the influence of valence, the discrimination of sad faces revealed most extensive hypoactivations although lacking any relatively increased brain activations and therefore possible compensatory activity. This was accompanied by remarkable impaired discrimination performance specificity for sad faces in juvenile patients.

Further investigations are required to clarify the role of such changes in brain activity in the development of the disease, the course of illness, and their influence on social and functional outcome in early onset schizophrenia.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare that no financial support or compensation has been received from any individual or corporate entity over the past 3 years that could have influenced this work and that there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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