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Psychiatry Research: Neuroimaging 122 (2003) 115–124
PSYCHIATRY RESEARCH
NEUROIMAGING
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Impairment in basal limbic function in schizophrenia during affect recognition

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Received 12 December 2001; received in revised form 16 August 2002; accepted 14 November 2002

Abstract

Patients with schizophrenia routinely fail to perform affect recognition tasks as accurately as healthy controls. The investigation of performance-related changes in cerebral activation in healthy subjects may facilitate the understanding of adaptation processes to different levels of difficulty and help to interpret the activation changes found in schizophrenic patients. Nine first hospitalized partly remitted schizophrenic patients and 10 healthy controls participated in an fMRI study with a facial affect discrimination and labeling task. Seven of the 10 healthy subjects were reexamined with changed stimulus conditions adapted according to the mean accuracy scores detected in schizophrenic patients. Controls showed a significantly increased activation of the right gyrus frontalis medialis with rising task difficulty during both tasks. The schizophrenic patients demonstrated a significantly decreased activation of the anterior cingulate during facial affect discrimination and of the amygdala–hippocampal complex bilaterally during facial affect labeling. In addition, an increased activation of the gyrus frontalis medialis bilaterally became apparent in the schizophrenic patients. It is suggested that the latter may reflect a compensatory effort for deficits in more basal limbic functions.

Keywords: Facial affect recognition; Schizophrenia; Functional magnetic resonance imaging

1. Introduction

Patients with schizophrenia appear to misinterpret social cues and exhibit difficulties in recognizing different aspects of the social milieu. Neuropsychological studies have indicated that these deficits may be at least partly related to disturbances in facial affect recognition (Mueser et al., 1997, for review). The latter is not a uniform phenomenon, but involves different processes among which facial affect discrimination and affect labeling are of particular importance (Schneider et al., 1995; Shaw et al., 1999).

The poor performance of schizophrenic patients has stimulated many investigators to examine these disturbances using various neuropsychological

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0925-4927/03/$ - see front matter
doi:10.1016/S0925-4927(02)00126-9

designs. Nevertheless, it is an unresolved problem whether the poor performance of schizophrenic patients reflects a specific deficit or a more generalized impairment of neuropsychological functioning. Deficits of affect recognition are unlikely to be caused by neuroleptic side effects, since they are also found in unmedicated schizophrenic patients. Moreover, longitudinal studies did not reveal a significant improvement of facial affect recognition within 1–3 month follow-up periods despite improvements in positive and negative symptoms (Gaebel and Wolwer, 1992; Addington and Addington, 1998) suggesting a trait character of the disturbances.

Results of functional imaging studies suggest that the neural network for recognizing emotion in visual input involves the prefrontal cortex, the anterior and posterior cingulate, the parietal cortex, the amygdala–hippocampal complex and the fusiform face area (George et al., 1993; Gorno-Tempini et al., 1998; Hariri et al., 2000). The only study investigating different subgroups of patients with schizophrenia demonstrated greater activation in visual cortex and insula in paranoid compared to non-paranoid patients in recognizing facial expressions (Phillips et al., 1999).

However, while previous functional magnetic resonance imaging (fMRI) studies have successfully characterized the 'where' of facial affect recognition, they have not addressed the dynamic range of physiological responses that presumably underlie variations in performance. Recent studies have demonstrated the potential impact of performance differences on cerebral activation changes in motor tasks and higher cognitive processes. Schröder et al. (1999) found that activation of the motor cortices increases with motor speed. A different activation pattern can be expected in higher cognitive processes, where a broad range of network components is involved. Callicott et al. (1999) were able to demonstrate an 'inverted-*U*' shaped neurophysiological response from lowest to highest load within the dorsolateral prefrontal cortex (DLPF) during a working memory task with increasing task difficulty. In contrast, regions outside of the DLPF often showed early plateau or continuously increasing responses that did not reflect performance effects. Based on these considerations, we hypothesized that prefrontal-derived functions within the facial affect recognition network would show performance-related responces, too.

According to the concept of hypofrontality (Buchsbaum, 1990; Schröder et al., 1994), one may expect a deficient activation of the frontal cortices and/or of associated cerebral regions during affect recognition. Furthermore, the question whether the respective deficits differ between the discrimination and the labeling conditions remains to be clarified.

However, repeated studies in patients are confounded by changes in psychopathology, compliance and medication status. Since patients with schizophrenia routinely fail to perform affect recognition tasks as accurately as healthy controls, it may be difficult to differentiate between performance- and disease-related activation changes. Therefore, the investigation of adaptation processes in healthy subjects to different levels of difficulty may facilitate the understanding of differences in neural network functioning in schizophrenic patients.

Following these questions, the aims of our study were: (1) investigation of cerebral activation in healthy subjects at different levels of difficulty in two tasks of facial affect recognition; (2) comparison with the results in first episode schizophrenic patients; and (3) deduction of implications for corresponding neuropsychological functions.

2. Methods

2.1. Subjects

Nine first hospitalized patients meeting DSM-IV criteria for schizophrenia and 10 healthy controls participated in the fMRI study. None of the patients had received neuroleptic treatment prior to the hospitalization. Patients were examined in a stabilized condition and received atypical neuroleptics (seven patients clozapine: mean dose = 270 ± 70 mg/day; two patients risperidone: each 4 mg/day). The experiments were approved by the local ethical committee, and written informed consent was obtained from the individual subjects. Exclusion criteria included a history of head injury,

Table 1
Clinical characteristics of patients and controls (median and range)

	Healthy controls $n=10$	Schizophrenic patients $n=9$
Age	28 (22–33)	26 (20–33)
Gender	M/F=6:4	M/F=4:5
Illness duration (months)	n.a.	13 (6–48)
PANSS Positive		13 (8–25)
PANSS Negative		18 (11–31)
PANSS Global		29 (21–43)
STAI X1		41 (36–46)
STAI X2		45 (34–52)

N.A.=not applicable

significant alcohol or drug abuse, and neurological disease. Psychopathological symptoms were assessed on the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). Patients with schizophrenia may exhibit anxiety during the fMRI experiment. To address these potential difficulties, the State-Trait Anxiety Inventory (STAI, Spielberger and Vagg, 1984) was administered immediately after the experiment (Table 1).

2.2. Experimental procedure

The subjects completed a blocked paradigm in which a control condition (inverted neutral faces as those are not predicted to engage emotion-processing areas) was compared to a stimulus condition consisting of different facial expressions (angry, happy, sad, disgusted, surprised and neutral). The stimuli used in this study were photographs developed by Ekman and Friesen (1976). A stimulation software package was created to project the faces on a screen using a LCD projector and a PC (Fig. 1). During image acquisition, subjects were in a supine position and viewed the screen through adjustable mirror glasses.

Task 1 was an emotion-matching task. Subjects were shown pairs of pictures of four different identities (two male and two female) and were asked to indicate by pressing a button with their right hand when the two pictures showed the same emotion. The pairs of pictures were shown in a randomized sequence with an average of 20% matches in the ON condition.

The second task was a facial affect labeling task. The subjects had to name the emotion displayed by one of four possible identities during the interstimulus interval to determine accuracy. Naming was performed in each control and stimulus condition out of the scanning periods (subjects were asked to say 'neutral' in the control condition, where neutral affects were presented) to reduce the speech-related activation. The experiments were explained to all subjects with an example of one block of each task prior to the scanning session.

To reduce the time of the whole experiment (and thus improve the compliance of patients), we varied the usual block design by reducing the control condition to half of its original length. Therefore, the blocked paradigm was designed as five control (30 s) and five stimulation (60 s) conditions for the stimulation protocol. Each pair of faces or the single face in the labeling task was shown for 4 s with an interstimulus interval of 2 s. The first 10 scanned volumes were excluded in both tasks because of the overshoot of hemodynamic response. Upon completion, 10 volumes of real baseline condition (blank screen without naming) were performed. This resulted in a total of 2550 images (170 volumes, 15 slices) in each experiment.

In a further experiment with identical acquisition parameters involving healthy subjects, the stimulus conditions were adapted according to the mean accuracy scores detected in the schizophrenic patients. To receive the same accuracy in healthy

Fig. 1. Pictures of facial affect (Ekman and Friesen, 1976) were fitted and implemented in the stimulation software; the affect-recognition tasks consisted of a discrimination task (left) and a labeling task (right).

subjects, the time of picture presentation had to be reduced to 2 s with a 1-s interstimulus interval. To avoid potential learning effects, the fMRI experiments were repeated at least 6 months after the initial session. However, only seven of the 10 healthy subjects initially included could be re-examined.

2.3. fMRI data acquisition and analysis

Functional imaging was performed at 1.5 Tesla (Picker EDGE, Cleveland, OH, USA) using the standard head coil and a single-shot, blipped gradient echo Echo-Planar-Imaging sequence (GE-EPI, volume of 15 slices, TR = 3000 ms, TE = 80 ms, FOV = 256 × 256 mm^2, voxel size = 1 × 1 × 5 mm^3). A high resolution T_1-weighted three-dimensional scan of the whole brain was recorded within the same scanning session for the overlay of functional and anatomical images (RF-spoiled FLASH sequence, TR = 30 ms, TE = 4.4 ms, voxel size = 1 × 1 × 1.3 mm^3). Data analyses including preprocessing, three-dimensional reconstruction, determination of Talairach coordinates and correlational analyses were performed using BrainVoyager® software (Goebel et al., 1998). Standard preprocessing, which consisted of detection and removal of the effects of small head movements, the reduction of high frequency spatial and temporal fluctuations, and the removal of low-frequency trends in the time courses of each pixel, was employed. For each subject, the structural three-dimensional data sets were transformed into Talairach space. The stimulation protocol served as a basis for appropriate reference specifying stimulus and control conditions (stimulus condition = 1, control condition = 0). Based on the parameters for importing two-dimensional functional slices into three-dimensional data sets and on parameters for transforming three-dimensional data sets into Talairach space, the complete functional data of each subject were transformed into Talairach space, yielding a four-dimensional data representation (volume time course = 3 × space, 1 × time). Prior to statistical analysis, a cluster size threshold of 90 voxels was defined as a spatial filter to reduce the number of false-positive entries into the activation map. The three-dimensional statistical maps (using correlation analysis with a threshold of $r < 0.3$) allowed us to determine Talairach coordinates of activated brain regions

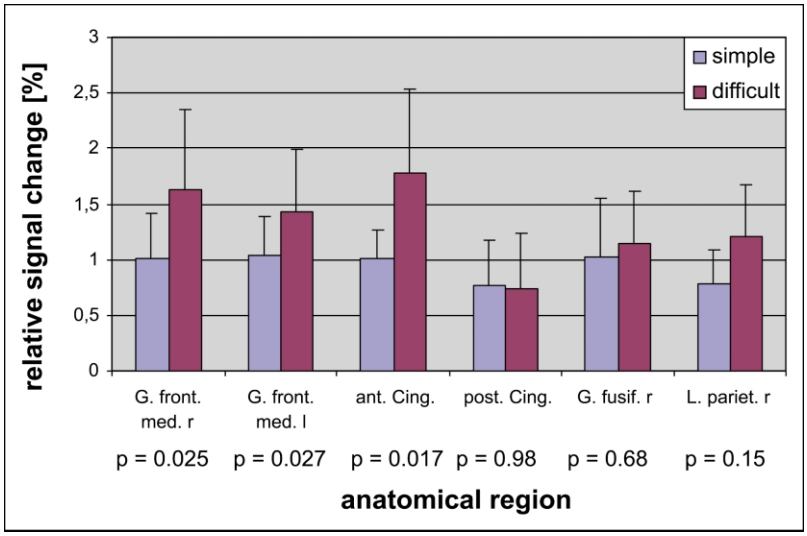

Fig. 2. Relative signal changes and S.D. of different anatomical regions during the discrimination task under simple and difficult conditions in healthy subjects (G. front. med. r/l = gyrus frontalis medialis right/left, ant. Cing. = anterior cingulate, post. Cing. = posterior cingulate, G. fusif. r = fusiform gyrus right, L. pariet. r = lobus parietalis right). *P*-values were estimated using Analysis Of Variance for repeated measurements (GLM) with the different conditions of difficulty as the within-subject factor.

and to display the BOLD signal time courses in these regions. In a second level analysis, the regions showing significant clusters of activation in all subjects were detected; regions with activation only in some subjects were excluded for further analysis. By linear reduction of the correlation window, a cluster of 90–120 voxels was determined as the volume of interest (VOI); thus only the clusters of strongest correlation were used for further statistical comparisons between the subjects.

The data for statistical comparisons consisted of the mean relative BOLD contrast of all marked voxels in these VOIs for each subject. For intra-individual comparisons (2 sessions for healthy controls), a repeated measures analysis of variance (SAS Institute Inc., Version 6, 1989) was performed, for independent variables (patients vs. controls), Student's *t*-test was used.

Values of relative signal change differing significantly between patients and controls were used for further detection of possible interactions between clinical parameters and cerebral activation. Therefore, correlation coefficients of patients' signal change values and the PANSS positive/negative scores as well as the number of errors during both tasks were calculated.

3. Results

3.1. Activation patterns in healthy subjects at different task difficulties

Group means and S.D. of relative signal change on both tasks are given in Figs. 2 and 3.

Healthy controls showed a mean accuracy score of 90% on both tasks in the initial experiment. After adaptation of stimulus conditions to the performance of schizophrenic patients, the mean accuracy score decreased to 75% on both tasks.

The discrimination task was associated with a pronounced activation of the gyrus frontalis medialis bilaterally, the anterior and posterior cingulate, the right fusiform gyrus and the right parietal lobe in all subjects. During the labeling task, additional activation of the amygdala–hippocampal complex bilaterally and the left fusiform gyrus, but no activation in the anterior cingulate, was observed.

Increased task difficulty in the second session was associated with quantitative signal changes in

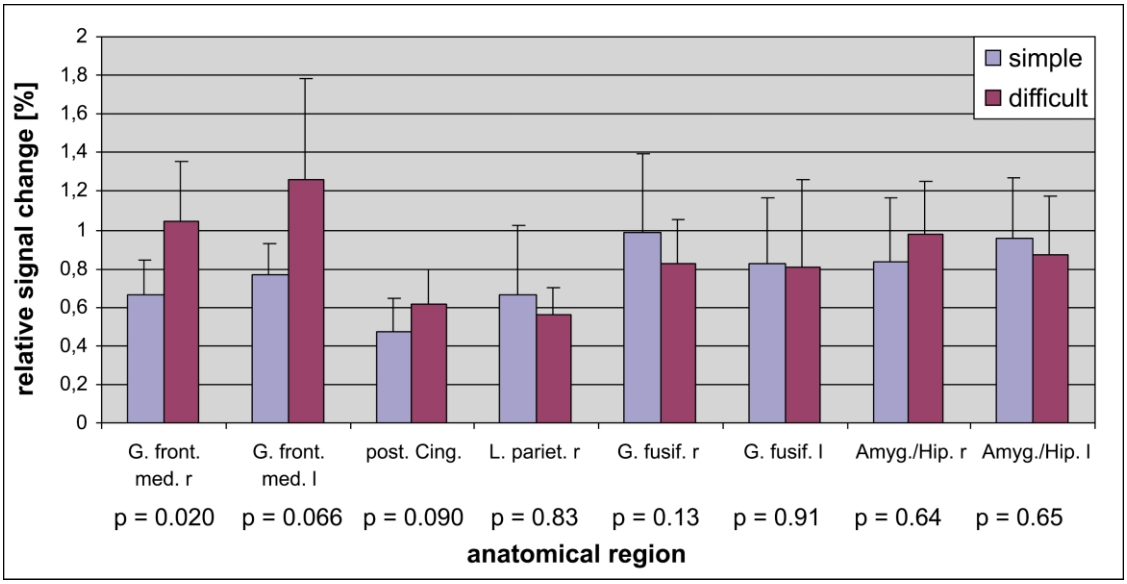

Fig. 3. Means and S.D. of relative signal changes in different anatomical regions during the labeling task under simple and difficult conditions in healthy subjects (G. front. med. r/l = gyrus frontalis medialis right/left, post. Cing. = posterior cingulate, G. fusif. r/l = fusiform gyrus right/left, L. pariet. r = lobus parietalis right). *P*-values were estimated using analysis of variance for repeated measurements (GLM) with the different conditions of difficulty as the within-subject factor.

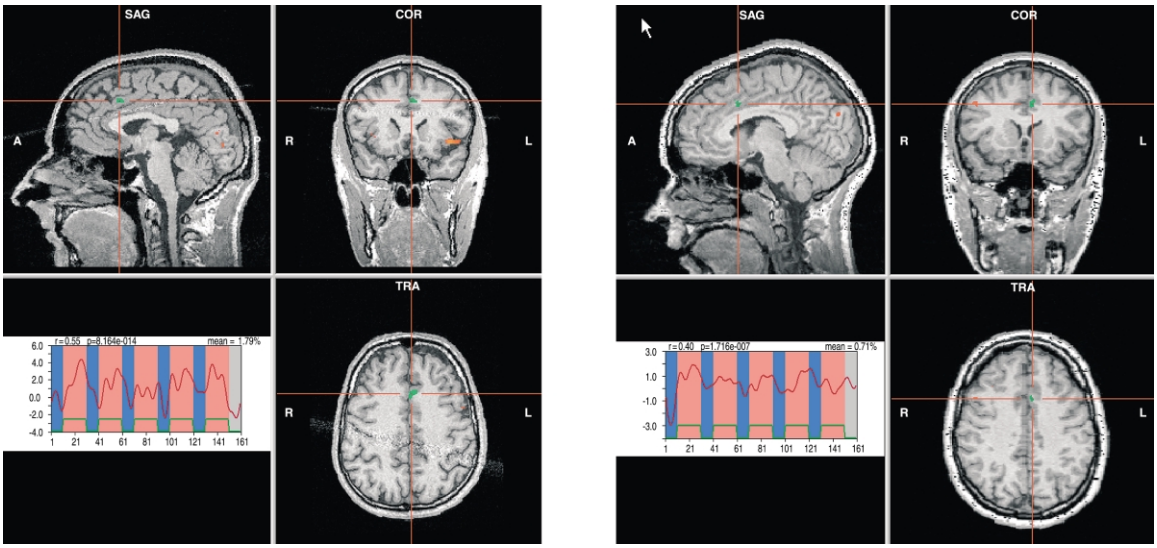

Fig. 4. Statistical Brainvoyager maps of a normal control (left) and a patient with schizophrenia (right) showing different activation patterns in the anterior cingulate during the discrimination task (relative signal change of 1.79 vs. 0.71). Results are projected on three two-dimensional planes. The images were thresholded at a correlation coefficent of $r > 0.3$ and a spatial extent criterion of $k = 90$ voxels. In addition, the corresponding signal time course (down left) of all marked voxels (red line) of the respective VOI and the reference function (green line) over the scanning period are presented.

Table 2
Results of discrimination task[a]

Anatomical region	Relative signal change, controls		Relative signal change, patients	Talairach coordinates (x, y, z)	P-value, controls vs. patients
	Simple	Difficult			
G. front. med. r	1.01±0.40	1.63±0.72	1.28±0.67	38, 4, 33	n.s.
G. front. med. l	1.04±0.34	1.43±0.56	1.39±0.95	−37, 1, 32	n.s.
ant. Cing.	1.01±0.26	1.78±0.76	0.70±0.31	6, 22, 32	<0.05
post. Cing.	0.77±0.40	0.73±0.50	0.51±0.22	7, −35, 16	n.s.
G. fusif. r	1.02±0.54	1.14±0.47	0.82±0.37	43, −50, −15	n.s.
L. pariet. r	0.79±0.30	1.21±0.47	0.71±0.36	28, −52, 42	n.s.

G. front. med. r/l = gyrus frontalis medialis right/left, ant. Cing. = anterior cingulate, post. Cing. = posterior cingulate, G. fusif. r = fusiform gyrus right, L. pariet. r = lobus parietalis right.

[a] Mean values and S.D. of relative signal change and mean Talairach coordinates in healthy controls and schizophrenic patients are presented in reference to the respective anatomical region. Findings are shown for controls during both simple and difficult stimulus conditions and in patients during the simple stimulus condition alone. Statistical P-values of significance testing (t-test, significance level: $P<0.05$) refer to activation during the same stimulus conditions in controls and patients.

the respective functional network. While the right gyrus frontalis medialis responded with significantly increased activation ($P<0.05$) during both tasks, significant activation increases in the anterior cingulate and the left gyrus frontalis medialis were only recorded during the discrimination task. No significant activation increases with greater task difficulty were found in the fusiform gyrus, the posterior cingulate, the right parietal lobe or the amygdala–hippocampal complex bilaterally.

3.2. Activation patterns in schizophrenic patients

Group means and S.D. of relative signal changes for patients and controls are given in Tables 2 and 3.

Compared with the healthy controls, the schizophrenic patients performed both tasks with a significantly lower accuracy (discrimination task: 75±6% vs. 90±8%; labeling task: 75±4% vs. 90±6%, $P<0.05$, respectively). During the dis-

Table 3
Results of labeling task[a]

Anatomical region	Relative signal change controls		Relative signal change patients	Talairach coordinates (x, y, z)	P-value controls vs. patients
	Simple	Difficult			
G. front. med. r	0.66±0.18	1.04±0.32	1.40±0.70	39, 1, 37	<0.01
G. front. med. l	0.77±0.16	1.26±0.52	1.18±0.64	−34, 3, 33	<0.05
post. Cing.	0.47±0.17	0.61±0.18	0.81±0.29	4, −39, 17	<0.05
L. pariet. r	0.66±0.36	0.56±0.14	0.56±0.25	32, −51, 30	n.s.
G. fusif. r	0.99±0.40	0.81±0.23	0.87±0.43	40, −44, −18	n.s.
G. fusif. l	0.82±0.35	0.80±0.45	0.89±0.27	−45, −48, −16	n.s.
Amyg./Hip. r	0.83±0.34	0.98±0.27	0.53±0.14	50, −24, 0	<0.05
Amyg./Hip. l	0.96±0.31	0.87±0.31	0.55±0.25	−44, −27, −5	<0.01

G. front. med. r/l = gyrus frontalis medialis right/left, post. Cing. = posterior cingulate, G. fusif. r/l = fusiform gyrus right/left, L. pariet. r = lobus parietalis right, Amyg/Hip. r/l = amygdala/hippocampus right/left.

[a] Mean values and S.D. of relative signal change and mean Talairach coordinates in healthy controls and schizophrenic patients are presented in reference to the respective anatomical region. Findings are shown for controls during both simple and difficult stimulus conditions and in patients during the simple stimulus condition alone. Statistical P-values of significance testing (t-test, significance level: $P<0.05$) refer to activation during the same stimulus conditions in controls and patients.

crimination task, patients with schizophrenia showed significantly ($P<0.05$) lower activation levels in the anterior cingulate than healthy subjects (Fig. 4). In addition, patients showed a trend ($P=0.15$ right vs. 0.16 left) towards higher activation levels in the gyrus frontalis medialis. Both groups showed only minor, non-significant differences in the other regions involved in the discrimination task.

The labeling task led to a significantly lower activation in the amygdala–hippocampal area bilaterally in the schizophrenic patients ($P<0.05$), whereas significantly higher activation values could be detected in the gyrus frontalis medialis bilaterally and the posterior cingulate in patients compared with controls during the same stimulus condition ($P<0.05$). The right parietal lobe and the fusiform gyrus bilaterally showed no significant differences between patients and controls.

Neither the total PANSS score nor any of the PANSS subscores was significantly correlated with cerebral activation. However, a significant correlation ($r=0.61$; $P<0.05$) between scores on the PANSS negative subscale and the number of errors during the discrimination task arose.

There was no evidence that the patients with schizophrenia exhibited anxiety during the fMRI experiment. Hence, STAI subscales for trait- and state-related anxiety did not show a significant difference. However, three additional patients had to be excluded since they terminated the experiment prematurely due to feelings of oppression.

4. Discussion

Our study provides three major findings: (1) healthy subjects showed a significantly increased activation of the right gyrus frontalis medialis with increased task difficulty; this effect applied to both the discrimination and the labeling tasks; (2) patients with schizophrenia were characterized by a significantly decreased activation of the anterior cingulate during facial affect discrimination and (3) of the amygdala–hippocampal complex bilaterally during facial affect labeling.

Our imaging data of healthy subjects indicate that the network underlying facial affect recognition adapts its function to deal with rising task demands. These observations parallel the findings of performance-related activation changes within distinct components of the respective cortical networks during motor and working memory tasks (Schröder et al., 1999; Callicott et al., 1999). We were able to demonstrate a stronger activation in the right gyrus frontalis medialis during the difficult condition, whereas the posterior cingulate, the fusiform gyrus, the right parietal lobe and the amygdala–hippocampal complex showed no performance-related responses in healthy subjects.

Compared with the healthy controls, the schizophrenic patients showed a poorer performance with a significantly decreased activation in the anterior cingulate during the discrimination task and in the amygdala–hippocampal complex during the labeling task, respectively. One may argue that comparison of these results with those obtained in the controls is limited by the poorer performance of the patients. However, the controls showed an increased or stable activation in the anterior cingulate and amygdala–hippocampal complex during the more difficult condition. Hence, it appears to be rather unlikely that the activation deficits found in the patients solely reflect performance-dependent changes.

While a decreased activation in cortical areas has often been directly attributed to disturbances of related neuropsychological functions, an increased activation raises the question of secondary effects. In our study, the schizophrenic patients showed an increased activation in the gyrus frontalis medialis bilaterally during both tasks. Increased activation values were also found in the controls during the more difficult task condition with degree of difficulty adjusted to the patient group. Thus, one may hypothesize that the increased activation of prefrontal areas refers to secondary mechanisms in the patients which compensate for disturbances in other functionally related cortical areas. These results appear to be generally consistent with models of redundancy in network organization and support the hypothesis that deficits of affect recognition in schizophrenia do not primarily reflect changes in the prefrontal cortices but of other functionally coupled areas. An exaggerated and inefficient level of prefrontal activity in schizophrenia may be an alternative

interpretation since recent studies have revealed an increased activation of the prefrontal cortex in schizophrenic patients compared to healthy controls during different working memory paradigms (Callicott et al., 2000; Manoach et al., 2000).

A recent study on conflict-related activity in the anterior cingulate during the continous performance test indicated a key role of this region in the evaluative process (Tamminga and Carter, 2000). According to the authors' model, the anterior cingulate regulates the adaptation to the constantly changing demands of the environment on a moment-to-moment basis by using conflict as an alerting signal. An automatic, 'moment to moment' processing within facial recognition and expression was earlier described by Hatfield et al. (1992) in the concept of 'primitive contagion'. The latter can be defined as 'the tendency to automatically mimic and synchronize movements, expressions, postures and vocalizations with those of another person and, consequently, to converge emotionally'. Recent findings by Wild et al. (2001) supported the hypothesis that emotional contagion is a fast process that is active in the duration range of normal facial expressions and that the emotion-evoking effect is stable and repeatable. Furthermore, the primitive emotional contagion is very likely to have a biologically 'prewired' neural basis because it acts rapidly, repeatedly and almost automatically. The data, however, did not permit further specification about the neurobiological correlates.

The activation decreases in anterior cingulate and amygdala/hippocampal regions during affect discrimination and affect labeling discussed above may refer to a basal limbic loop that is disturbed in schizophrenic patients. In our view, an afference copy from the heteromodal cortex may stimulate this basal limbic loop and interfere with the conscious processing of prefrontal and parietal cortices. As a consequence of this dysfunction, cognitive compensation mechanisms evolve with stronger demands on prefrontal functioning.

The concept of a disturbed primitive emotional contagion may also explain the impairment in affect attunement, which is commonly found in schizophrenic patients. Affect attunement depends on the intact ability to recognize and to interpret the emotions expressed by others. Shaw et al. (1999) demonstrated the clinical significance of the consequently misattuned responses in schizophrenic subjects that led the rater to assess inappropriate affect.

Significant correlations between psychopathological symptoms and cerebral activation could not be found. With respect to neuropsychological performance, only the number of errors during the discrimination task was correlated with negative symptoms. The fact that the present study did not replicate the significant association between negative symptoms and decreased activation values in the anterior cingulum (Schneider et al., 1995; Schröder et al., 1996) is clearly related to the small sample size. The latter also prevented us from differentiating primary and secondary negative symptoms that might have led to additional results. To show the dynamic nature of prefrontal changes in the patients, a second experiment with adaptation of the paradigm to the accuracy scores in healthy subjects would have been useful. Two experiments within the same clinical period often lead to more dropouts, but the problem may be overcome if only one task with a shorter scanning time is used.

In conclusion, our study showed that healthy subjects compensate for rising task demands in different facial affect recognition tasks with an increased activation of the prefrontal cortices. The poor performance of schizophrenic patients can be related to disturbed components of the neural network involved; among these, the anterior cingulate and the amygdala–hippocampus complex may be of particular importance. This limbic dysfunction may represent the neural basis of a disturbed primitive emotional contagion in schizophrenic patients, which correspond to impairment in affect recognition on the neuropsychological level and inappropriate affect on the symptoms level. The increased activation of the gyrus frontalis medialis in the schizophrenic patients may reflect internal cognitive coping strategies in response to deficits in more basal limbic functions.

Acknowledgments

We thank C. Bottmer/Heidelberg, M. Backenstrass/Heidelberg and one anonymous reviewer for their critical remarks and valuable suggestions.

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