Regular Article

Psychotherapy and Psychosomatics

Psychother Psychosom 2010;79:363–370
DOI: 10.1159/000320121

Received: November 2, 2009
Accepted after revision: March 2, 2010
Published online: August 20, 2010

Increased Activation of the Supragenual Anterior Cingulate Cortex during Visual Emotional Processing in Male Subjects with High Degrees of Alexithymia: An Event-Related fMRI Study

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Key Words

Emotion · Alexithymia · Supragenual anterior cingulate cortex · TAS-20, fMRI

Abstract

Background: One of the most prominent neurobiological models of alexithymia assumes an altered function of the anterior cingulate cortex (ACC) as the crucial neural correlate of alexithymia. So far functional imaging studies have yielded inconclusive results. Therefore, we tested this hypothesis in healthy alexithymics and nonalexithymics in an event-related fMRI study. ***Methods:*** Thirty high- and 30 low-alexithymic right-handed male subjects (selected by the 20-item Toronto Alexithymia Scale, TAS-20) were investigated with event-related fMRI using a picture viewing paradigm. The stimuli consisted of happy, fearful and neutral facial expressions (Ekman-Friesen) as well as positive, negative and neutral pictures from the International Affective Picture System. ***Results:*** Contrasting the high-alexithymic with the low-alexithymic group we observed increased activation of the supragenual ACC for different emotional valences as well as for different emotional stimuli. Moreover, there was a positive correlation of the ACC with the individual TAS-20 scores but no correlations with the individual Beck Depression Inventory scores. Additionally, there was no difference in activity of the amygdala. ***Conclusions:*** We demonstrated that the supragenual ACC is constantly activated more strongly in alexithymic subjects and that this activation is related to the symptoms of alexithymia and not to associated symptoms such as depression. Therefore, our findings support the hypothesis of an altered function of the ACC in alexithymia.

Introduction

Alexithymia is a personality construct that is predominately characterized by difficulties in identifying and describing subjective feelings or emotional aspects of social interactions [1–3]. Moreover, alexithymia is associated with an enhanced risk of psychological impairment including chronic pain, somatoform disorders, addictive disorders, anxiety and depression [3–7]. Several neuro-

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biological models of alexithymia have been proposed [4–6]. For example, based on observations in split-brain patients a reduced interhemispheric communication was postulated [1]. Another model involves dysfunction of the right hemisphere evidenced by the fact that highly alexithymic individuals and patients with right hemisphere lesion show difficulties in recognizing facial expressions of emotions [2, 3]. We focus on the anterior cingulate cortex (ACC) deficit model [7] since it is supported by functional imaging studies on healthy subjects [8–11] as well as by lesion studies [12–16] and has been in the focus of neuroimaging studies on alexithymia [4, 17–19]. According to this model, alexithymia is associated with impoverished conscious experience of emotion caused by an altered function of the ACC. There are 3 functional imaging studies comparing visual emotional processing in male subjects with high versus low degrees of alexithymia, yielding inconclusive results. Berthoz et al. [20] found a greater activation in the ACC for men with high degrees of alexithymia. However, the differences were dependent on the emotional valence of the stimuli. Additionally, Kano et al. [8] found decreased activation for angry but not for sad or happy facial stimuli, and Leweke et al. [21] observed decreased activation for disgusted but not for fearful facial stimuli. A central feature of the altered ACC hypothesis is that subcortical limbic structures remain unaffected [9]. In accordance with this assumption, Berthoz et al. [20] and Kano et al. [8] did not observe any differences in the limbic structures. However, Leweke et al. [21] reported lower activations of the right amygdala for alexithymic subjects. This was confirmed by recent studies on healthy volunteers demonstrating a negative correlation of activity in the amygdala with scores on the 20-item Toronto Alexithymia Scale (TAS-20) [22, 23]. The aim of our study was to test the ACC deficit model in well-defined homogeneous samples, thereby controlling for the influence of possible coexisting depressive features assessed by the Beck Depression Inventory (BDI) [24]. Based on previous results we expected altered neural processing in ACC, but not in amygdala, as well as a significant correlation of the ACC with sum scores of the TAS-20.

Methods

Participants

Classification was based on the sum score of the Toronto Alexithymia Scale (German 20-item version, TAS-20 [25–27]). High and low alexithymia was defined a priori with reference to a random sample of adults [28]. The 33rd (sum score = 45) percentile was used as a cutoff for low alexithymia and the 66th (sum score = 52) for high alexithymia [28, 29]. Moreover, all subjects completed the German version of the BDI [30]. Subjects with clinically relevant depression (BDI >12) were excluded. In order to achieve a high level of homogeneity among the groups, we only included male subjects aged between 20 and 40 years with a German high school diploma. Thirty high- and 30 low-alexithymic subjects participated in this study. They were thoroughly questioned by means of a semistructured clinical questionnaire. It consists of the inhouse anamnestic sheet from the Psychophysiological Laboratory at the Clinical Institute of Psychosomatic Medicine (University of Düsseldorf) that was used in order to control for exclusion criteria such as history of psychiatric, neurological, severe medical illness or use of psychoactive substances. The same questionnaire was also used by Franz et al. [2]. Thirty high- and 30 low-alexithymic subjects participated in this study. They were all right-handed as assessed by the Edinburgh Inventory for Handedness [31]. After a detailed explanation of the study design and any potential risks, all subjects gave their written informed consent. The study was approved by the institutional ethics board of the University of Düsseldorf/Germany.

Paradigm

We used 50 fearful, 50 happy and 50 neutral images of facial affect from the Ekman-Friesen inventory [32] as well as 50 positive, 50 negative and 50 neutral images taken from the International Affective Picture System (IAPS) [33]. The affective ratings of the selected IAPS pictures have been determined by the pleasure ratings of the IAPS. Positive pictures had norm ratings of 7–9, neutral pictures had norm ratings of 4–6 and negative pictures had norm ratings of 1–3 [34]. Since the Ekman-Friesen inventory does not contain enough pictures for 150 presentations, the same pictures were presented 3 or 4 times. The IAPS pictures were only presented once.

The aim of this paper was to focus on emotional processing. In order to inhibit neural activations associated with cognitive processing, we used a picture viewing task [34–36]. The subjects were explicitly instructed to only passively view and not to judge the pictures. Moreover, to control for a constant level of attention, they had to press a button with their right index finger as soon as they recognized the picture appear on the screen.

All the IAPS and the Ekman-Friesen pictures were presented for 4 s each. Reaction times (time from appearance of the picture to pressing the button) were recorded. After the presentation of the picture, a fixation cross was shown for 6–8 s (6.0, 6.5, 7.0, 7.5 or 8.0 s randomly varied). The fixation cross was centered on a black background. The different types of IAPS and Ekman-Friesen pictures were pseudorandomized within and across the runs. During fMRI, the pictures were presented on a monitor inside the scanner room.

Behavioral Analyses

Reaction times for the IAPS and the Ekman-Friesen stimuli were analyzed in two 2-factorial analyses of variance with repeated measurements with the between-subjects factor group (nonalexithymic subjects/alexithymic subjects) and within-subjects factor affect (positive/negative/neutral pictures) for the first analysis, as well as with the between-subjects factor group (nonalexithymic subjects/alexithymic subjects) and the within-subject factor affect (happy/fearful/neutral) for the second analysis. These analyses were performed with SPSS, version 15.0.

fMRI

MR measurements were performed on a 1.5-tesla Siemens Sonata scanner by using a standard head coil (at Forschungszentrum Jülich, Germany). To enhance the statistical inference in subcortical brain regions with special focus on the amygdala we applied the scanning procedure described in detail by Stocker et al. [37]. Image processing and statistical analyses were carried out using MATLAB 7.4.0 and SPM5 (http://www.fil.ion.ucl.ac.uk). The images were corrected for differences in slice acquisition time, realigned to the first volume of the time series to correct for between-scan movement, corrected for motion artifacts, mean-adjusted by proportional scaling, resliced and normalized into standard stereotactic space (cluster size = $2 \times 2 \times 2$ mm^3) using a nonlinear discrete cosine transform and smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency drifts (cutoff = 128 s). The intraindividual first-level analysis used the general linear model [38]. The design matrix included regressors encoding negative, positive and neutral IAPS as well as fearful, happy and neutral facial expressions. Moreover, for each experimental run, the 6 parameters obtained in the realignment procedure were included as covariates of no interest in the design matrix. After defining the first-level models subject-specific activations were calculated using contrasts of each regressor against baseline. These contrasts were then passed to a second-level random effects analysis. Finally, for between-group analyses 2-sample t tests were calculated comparing alexithymic and nonalexithymic subjects for the following contrasts.

IAPS pictures: negative stimuli versus baseline, positive stimuli versus baseline, neutral stimuli versus baseline, and negative + positive stimuli versus baseline.

Ekman-Friesen pictures: happy faces versus baseline, fearful faces versus baseline, neutral faces versus baseline, and happy + fearful faces versus baseline.

IAPS + Ekman-Friesen pictures: positive IAPS stimuli + happy faces versus baseline, negative IAPS stimuli + fearful faces versus baseline, neutral IAPS stimuli + neutral faces versus baseline, and all emotional IAPS and Ekman-Friesen stimuli versus baseline.

Moreover, we performed regression analyses with the contrast images from the emotional IAPS and Ekman-Friesen stimuli and the individual sum scores of the TAS-20 and the BDI. The regression analyses were done with the following contrasts: negative IAPS stimuli versus baseline, positive IAPS stimuli versus baseline, negative + positive IAPS stimuli versus baseline, happy faces versus baseline, fearful faces versus baseline, happy + fearful faces versus baseline, positive IAPS stimuli + happy faces versus baseline, negative IAPS stimuli + fearful faces versus baseline, and all emotional IAPS and Ekman-Friesen stimuli versus baseline.

The statistical threshold for significant activations was set to $p < 0.05$ FDR-corrected for multiple comparisons with an additional cluster size threshold of $k > 10$. To test explicitly for activations in the amygdala and the ACC, we also used a hypothesis-driven region-of-interest (ROI) approach for all contrasts and all regression analyses. We first performed the whole-brain analyses thresholded at $p < 0.001$ uncorrected with $k > 10$ voxels. Then we conducted the ROI analysis for ACC and amygdala [39]. ROIs were defined using the AAL regions of the WFU Pick Atlas version 1.02 [40]. Again, the second-level significance threshold was set to $p < 0.05$ FDR-corrected and $k > 10$. For the correlation analyses we only report significant results for the predefined ROIs.

Results

The averaged TAS-20 sum and BDI scores for the subjects with low degrees of alexithymia were 33.32 (SD = 5.62) and 2.61 (SD = 2.43), whereas for the subjects with high degrees of alexithymia they were 59.06 (SD = 5.43) and 6.06 (SD = 3.10). The low-alexithymic subjects were aged 27.1 years (SD = 4.8) and the high-alexithymic subjects 26.6 years (SD = 4.2). The groups differed significantly in the TAS-20 (t test $p < 0.001$) and the BDI (t test $p < 0.001$) but not age (t test $p = 0.359$). However, concerning the intergroup differences in BDI it should be added that both the low- and the high-alexithymic subjects scored far below the threshold of 12. Therefore, both groups were characterized as not depressive by the BDI.

Behavioral Results

IAPS Stimuli

The alexithymic subjects had the following mean reaction times: negative stimuli 1,318 ms (SD = 507), positive stimuli 1,228 ms (SD = 434) and neutral stimuli 1,120 ms (SD = 376). The results for the nonalexithymic subjects were as follows: negative stimuli 1,210 ms (SD = 510 ms), positive stimuli 1,123 ms (SD = 463 ms) and neutral stimuli 1,025 ms (SD = 407 ms). The analysis of variance revealed no significant difference between alexithymic and nonalexithymic subjects. However, there was a significant difference with regard to the effect of the type of stimulus ($F = 41.84$, d.f. = 2/110, $p < 0.0001$) on reaction times. Post hoc t tests demonstrated a significant difference between the reaction times for negative versus positive, positive versus neutral and negative versus neutral stimuli ($p < 0.001$).

Ekmann-Friesen Stimuli

The alexithymic subjects had the following mean reaction times: fearful faces 1,119 ms (SD = 489), happy faces 1,038 ms (SD = 371) and neutral faces 1,104 ms (SD = 484). The results for the nonalexithymic subjects were: fearful faces 969 ms (SD = 424), happy faces 961 ms (SD = 404) and neutral faces 942 ms (SD = 384). The analysis of variance revealed neither a significant difference between alexithymic and nonalexithymic subjects nor any significant effect with regard to the type of stimulus.

Table 1. Results of ROI analyses (ACC) comparing subjects with high and low degrees of alexithymia referring to the following contrasts

Contrasts	Z score	MNI coordinates			p (FDR-corr.)	Cluster
		x	y	z		
IAPS stimuli						
Positive	3.03	8	24	27	0.001[1]	14
Negative	4.05	–2	40	17	<0.001[1]	25
	3.58	8	28	21	<0.001[1]	19
Positive + negative	4.54	8	26	25	0.009	59
	3.81	–6	36	21	0.011	32
Ekman-Friesen faces						
Happy	3.51	–4	38	23	<0.001[1]	12
Fearful	3.64	6	26	23	0.047	45
Happy + fearful	4.64	–4	38	23	0.003	269
Faces + IAPS						
Happy + positive	4.05	–6	36	21	0.034	28
	3.46	10	18	27	0.042	26
Fearful + negative	4.62	6	26	25	0.001	374
All emotional stimuli	5.67	8	26	25	<0.001	587
	3.96	14	40	5	<0.001	26

IAPS stimuli: viewing of emotional IAPS pictures compared to baseline with positive, negative and positive + negative pictures. Ekman-Friesen faces: viewing of emotional facial expressions compared to baseline with happy, fearful and happy + fearful faces. Faces + IAPS: viewing of emotional facial expressions + emotional IAPS pictures compared to baseline with positive emotional stimuli (happy faces + positive IAPS pictures), negative emotional stimuli (fearful faces + negative IAPS pictures) and positive + negative emotional stimuli. The presented values refer to the peak voxels (= voxel in a cluster that has the highest test statistic). See also figure 1 for illustration. [1] Uncorrected p value.

fMRI Results

IAPS Pictures

The between-group comparisons of subjects with low degrees of alexithymia versus those with high degrees showed no significant differences for negative emotions, positive emotions or the main effect of positive and negative emotions.

In contrast, all emotional stimuli induced stronger activations in the ACC of the alexithymic subjects in the reversed between-group contrast alexithymics versus non-alexithymics (table 1 and fig. 1 depicting results of the ACC ROI analysis). Additionally, the following activations were found in the whole brain analysis.

Negative stimuli: subjects with high degrees of alexithymia showed stronger activation in the insula (x = –44, y = 4, z = 9; Z = 4.94), medial frontal gyrus (x = –2, y = 26, z = 45; Z = 4.76), superior temporal gyrus (x = 60, y = –46, z = 13; Z = 4.19), lingual gyrus (x = 12, y = –80, z = 3; Z = 4.97), cuneus (x = –8, y = –74, z = 9; Z = 4.25) and cerebellum (x = 34, y = –56, z = –31; Z = 3.99).

Positive stimuli evoked no additional significant difference between the groups.

Positive + negative stimuli: as the main effect of emotional pictures, subjects with high degrees of alexithymia showed stronger activation in the insula (x = –42, y = 4, z = 7; Z = 5.61), inferior frontal gyrus (x = –28, y = 30, z = 3; Z = 4.23), middle temporal gyrus (x = –60, y = 0, z = –13; Z = 5.05), superior temporal gyrus (x = –58, y = –44, z = 11; Z = 5.03), parahippocampal gyrus (x = 20, y = –54, z = –1; Z = 4.03), lingual gyrus (x = 10, y = –78, z = 3; Z = 5.97) and middle occipital gyrus (x = –20, y = –92, z = 11; Z = 4.11).

There was no significant difference between the groups with respect to activations evoked by neutral pictures.

Ekman-Friesen Pictures

The between-group comparisons of subjects with low versus high degrees of alexithymia showed no significant differences for fear, happiness or the main effect of emotional faces. In the reversed contrast of alexithymic ver-

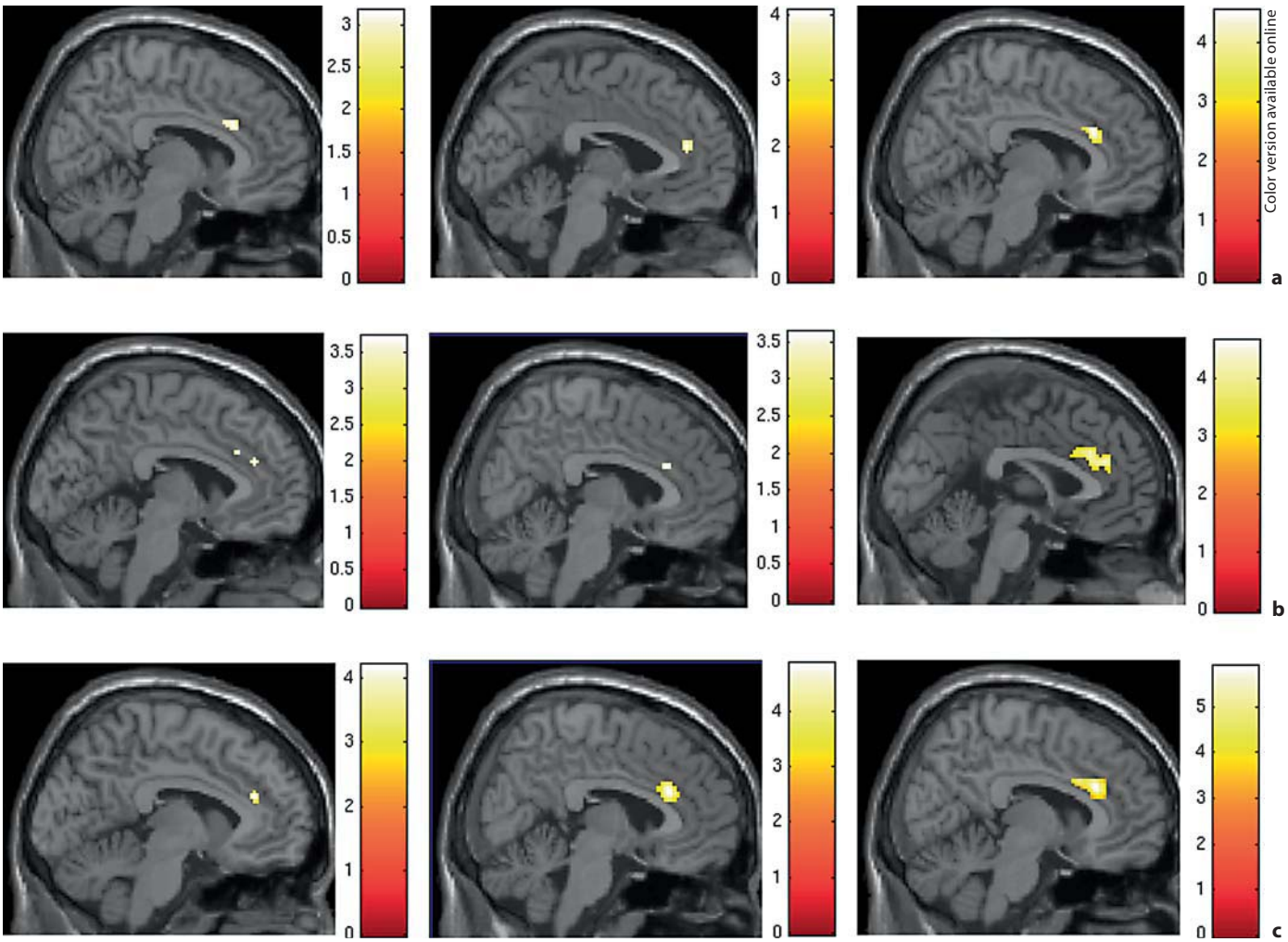

Fig. 1. Statistical parametric (T) maps of ROI analyses (anterior cingulate cortex) for alexithymic versus nonalexithymic subjects. **a** IAPS stimuli: viewing of emotional IAPS pictures compared to baseline with positive pictures (left), negative picture (middle) and positive + negative pictures (right). **b** Ekman-Friesen faces: viewing of emotional facial expressions compared to baseline with happy faces (left), fearful faces (middle) and happy + fearful faces (right). **c** Faces + IAPS: viewing of emotional facial expressions + emotional IAPS pictures compared to baseline with positive emotional stimuli (happy faces + positive IAPS pictures; left), negative emotional stimuli (fearful faces + negative IAPS pictures; middle) and positive + negative emotional stimuli (right). Clusters are displayed with $p < 0.001$ uncorrected and $k > 10$ voxel threshold. See table 1 for exact coordinates.

sus nonalexithymic subjects, all emotional stimuli induced stronger ACC activation in alexithymics (table 1 and fig. 1 depicting results of the ACC ROI analysis). Additionally, the following activations were found in the whole-brain analysis.

Happy + fearful stimuli: the main effects for emotional faces showed additional activations in the insula (x = –38, y = 10, z = 21; Z = 4.48), middle frontal gyrus (x = 36, y = 42, z = 27; Z = 5.87), inferior frontal gyrus (x = 42, y = 12, z = 21; Z = 4.93), inferior parietal lobule (x = 42, y = –40, z = 27; Z = 4.93) and middle occipital gyrus (x = 26, y = –84, z = –3; Z = 3.96) for subjects with high degrees of alexithymia (whole-brain analysis).

However, no additional significant activation was found for the separate effects of fearful or happy faces.

There was no significant group difference with respect to activations evoked by neutral pictures.

Main Effect of IAPS and Ekman-Friesen Pictures

The between-group comparisons of subjects with low versus those with high degrees of alexithymia revealed no significant differences for positive emotional stimuli

Table 2. Positive correlations of emotional picture viewing (Ekman-Friesen + IAPS) with individual TAS-20 sum scores (ROI: ACC)

Positive correlations	Z score	MNI coordinates			p (FDR-corr.)	Cluster
		x	y	z		
IAPS stimuli						
Positive + negative	4.24	8	26	25	0.016	51
	3.95	4	48	27	0.018	13
Ekman-Friesen faces						
Happy + fearful	3.79	0	36	23	<0.001[1]	34
Faces + IAPS						
Happy + positive	no significant correlation					
Fearful + negative	3.89	8	26	25	0.028	84
All emotional stimuli	4.35	8	26	25	0.007	199
	3.73	12	42	5	0.008	19

Activations are only reported if they survived a threshold of $p < 0.001$ uncorrected and $k > 10$ referring. The presented values refer to the peak voxels. [1] Uncorrected p value.

(happy facial expressions and positive IAPS pictures), for negative emotional stimuli (fearful facial expressions and negative IAPS pictures), or for the main effect of emotion (positive + negative IAPS and happy + fearful Ekman-Friesen stimuli). Vice versa, the between-group contrast of alexithymics versus nonalexithymics demonstrated stronger activation in the ACC of the alexithymic subjects (table 1 and fig. 1). Additionally, the following activations were found.

Negative emotional stimuli: increases in the blood-oxygenation-level dependent signal in subjects with high degrees of alexithymia were found in the insula (x = 38, y = 8, z = 19; Z = 4.49), middle frontal gyrus (x = 34, y = 42, z = 25; Z = 4.54), inferior frontal gyrus (x = –38, y = 8, z = 23; Z = 4.10), superior temporal gyrus (x = –48, y = 6, z = 1; Z = 4.77), cuneus (x = –4, y = –72, z = 7; Z = 4.69), claustrum (x = –34, y = –12, z = 5; Z = 3.80) and caudate (x = –20, y = –14, z = 21; Z = 3.85).

Positive emotional stimuli evoked no additional significant group differences.

Positive + negative emotional stimuli: the main effect of emotional pictures demonstrated activations in the bilateral insula (x = –42, y = 6, z = 7; Z = 5.73 and x = 40, y = 10, z = 19; Z = 5.79), middle frontal gyrus (x = 36, y = 42, z = 27; Z = 6.16), inferior frontal gyrus (x = –40, y = 8, z = 23; Z = 5.42), superior temporal gyrus (x = 58, y = –46, z = 9; Z = 5.30), lingual gyrus (x = 6, y = –86, z = 25; Z = 5.94), middle occipital gyrus (x = –20, y = –90, z = 9; Z = 4.78), cuneus (x = 6, y = –86, z = 25; Z = 5.04) and cerebellum (x = 34, y = –56, z = –31; Z = 4.85).

There was no significant group difference with respect to activations evoked by neutral pictures.

ROI analyses: the ROI analyses of the ACC have been described above (table 1, fig. 1). None of the contrasts (IAPS picture, Ekman-Friesen pictures or Ekman-Friesen and IAPS pictures) resulted in any difference in activation in the amygdala either for high alexithymia versus low alexithymia or for low alexithymia versus high alexithymia even following small volume correction.

Correlation Analyses

For the contrasts 'main effect of emotional IAPS stimuli versus baseline', 'main effect of emotional faces versus baseline', 'main effect of negative emotional stimuli versus baseline' and 'main effect of all emotional stimuli versus baseline' TAS-20 sum scores showed positive correlations with activity in the ACC (table 2).

The ACC showed no significant correlation with the BDI sum scores. Additionally, activity in the amygdala did not correlate with TAS-20 or BDI sum scores even following small volume correction.

Discussion

Our results revealed different neural activations in high-alexithymic subjects separately and combined for happy and fearful facial expressions, separately and com-

bined for positive and negative IAPS pictures as well as for combined processing of emotional IAPS and Ekman-Friesen pictures. Thus, an alteration in ACC activity was constantly observed for different types of visual emotional stimuli as well as for different valences. Furthermore, viewing of emotional pictures correlated positively with the individual TAS-20 scores but not with BDI scores in ACC. These results are in accordance with functional imaging studies demonstrating the role of the ACC in emotional processing and emotional consciousness [11, 12, 41] as well as with findings from lesion studies [14, 15, 17, 18, 42]. However, in contrast to Lane et al. [9], we observed a stronger activation in the ACC of alexithymic subjects. This difference might be due to the fact that they used the Levels of Emotional Awareness Scale instead of the TAS-20. Our findings are supported by Meriau et al. [43] reporting a positive correlation of the TAS-20 with activity in the ACC. Berthoz et al. [20] found stronger activation in ACC of alexithymic subjects for positive but not for negative IAPS stimuli. We also found activations for positive stimuli in ACC but additionally activation for negative stimuli. The diverging results might in part be explained by their small sample size and the fact that they only report results for stimuli with high arousal values. Although Leweke et al. [21] and Karlsson et al. [44] found altered activity in similar parts of the ACC compared to our results, they observed hypoactivation in high-alexithymic subjects. Leweke et al. [21] included subjects with psychosomatic diseases. Therefore, their results are difficult to compare with healthy subjects. Karlsson et al. [44] used film clips as stimuli which are more complex than single pictures. It might be speculated that films induce different neural processing due to their prolonged engaging nature. Studies directly comparing complex and simple emotional stimuli are needed to decide on a possible influence on the ACC activation in high-alexithymic subjects. In line with other neuroimaging studies [8, 20] we did not find evidence for an altered function of the amygdala in alexithymic subjects. One of the reasons that others did find involvement of the amygdala might be related to gender difference of the investigated samples. Our sample and those of Berthoz et al. [20] and Kano et al. [8] consisted only of male subjects, whereas Reker et al. [23] investigated only female subjects and Leweke et al. [21] as well as Kugel et al. [22] had a mixed sample. Additionally, since the Ekman-Friesen pictures were repeatedly presented, our failure to find amygdala activation might also have been due to a habituation of the amygdala over time [45]. Finally, we did not find significant activation in the contrast low versus high alexithymia in the subtraction analysis. Therefore, no region showed stronger activation in the group of the low-alexithymic subjects. The observed activations for the opposite contrast (i.e. high versus low) may be caused by increased activation in the high-alexithymic group or by decreased activation in the low-alexithymic group which cannot be further disentangled by the present set of data analyses.

Acknowledgment

The study was financially supported by a grant from the Forschungskommission der Medizinischen Fakultät of Heinrich Heine Universität Düsseldorf to A.H.

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