Attentional modulation of emotional stimulus processing in patients with major depression—Alterations in prefrontal cortical regions

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Patients with depression show an impaired ability to modulate emotional states and to process positive emotional information. Here we examined expectancy-induced modulation of emotional picture processing in major depression. We hypothesized alterations in the medial prefrontal cortex. During fMRI, 15 depressed and 21 healthy control subjects passively viewed affective photographs. Half of the pictures were preceded by an expectancy cue signaling whether an emotionally salient or neutral picture would follow. The contrast 'cued versus uncued emotional picture viewing' was used to study modulation of emotional picture processing by preceding attention. Healthy individuals showed enhanced activation in the dorsomedial prefrontal cortex and decreased activation in the dorsolateral prefrontal cortex during cued compared to uncued emotional picture perception. The group comparison revealed that these modulatory effects were significantly attenuated in depressed patients. This attenuation was particularly observed in the positive compared to the negative picture condition and tended to normalize in the dorsomedial prefrontal cortex after remission of symptoms. Altered prefrontal modulation in depression may contribute to impaired affect modulation and related clinical symptoms, such as anhedonia.

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Patients with depression show a deficit in emotion modulation. This is reflected in sustained depressed mood, rigid affect, and reduced emotional reactivity to both positive and (to a lesser extent) negative stimuli [7]. In addition, depressed patients show deficits in processing positive emotional contents, as reflected in anhedonia and a negative attentional bias [7,18].

While a number of neuroimaging studies have examined the deficits in processing positive contents [18], little is known about the modulation of emotional responses in depression [4,12,15,27]. Studies in healthy individuals implicate the prefrontal cortex in this process [5,20].

Here we explored the role of the prefrontal cortex in attentional modulation of emotional picture processing in major depression using a previously established emotional expectancy paradigm [5]. In contrast to several previous expectancy studies [1,6,14], we did not focus on the actual expectancy period. The comparison of interest was 'cued versus uncued emotional picture perception'. Signaling an emotionally salient picture, the expectancy cue induced 'preceding' attention to the emotional content of the subsequent picture [23], thus modulating the perception of the picture.

In healthy individuals, emotional expectancy augments the neural response to emotional pictures in the dorsomedial prefrontal cortex (DMPFC) [5]. Applying the paradigm to depressed patients, we tested the following hypotheses: first, depressed patients would exhibit altered attentional modulation of emotional picture processing. Based on our own findings [5] and on neuroimaging studies in depressed patients [21,27], we expected dorsal prefrontal abnormalities. Second, because of the negative processing bias, we hypothesized that altered modulation would differentially affect the positive and negative picture conditions.

Fifteen patients with major depression (Table 1) and 21 healthy controls completed the experiment. Patients were hospitalized in the Department of Psychiatry at the Otto-von-Guericke University Magdeburg. Healthy controls (10 female, mean age ± S.D. 24.1 ± 2.5, range 21–31) had no psychiatric axis I or II disorder (SCID). Study groups differed with regard to age (T = 7.2; p < 0.001). All participants were right-handed.

The diagnosis of major depression was established using the SCID and case note review. Patients had no concurrent Axis I disorder and their 21-item Hamilton Depression Rating Scale (HDRS) score

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was \( \geq 18 \). Two patients had bipolar depression and two patients showed psychotic features. Nine patients reported an affective disorder in a first-degree relative. Five patients (4 female; mean age 42.6 years) were exploratorily investigated for a second time (t2) after remission (HDRS score \( \leq 8 \)). The average time interval between t1 and t2 was 6.2 weeks (range 5–8 weeks). The five patients studied at t2 were treated with mirtazapine (3), venlafaxine (1), tricyclic antidepressants (1), atypical antipsychotics (3), tricyclic antipsychotics (1), and promethazine (2).

Exclusion criteria were current neurological or severe medical disorder, history of closed head injury resulting in loss of consciousness, age below 18 or above 65 years, or contraindications to fMRI. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local research ethics committee.

The study used the modified version of a paradigm studied earlier in healthy subjects [5]. During fMRI, subjects saw emotional pictures for 5 s [17]. Half of the emotional pictures were preceded by emotional expectancy cues (upright arrow, 4 s), the other half was not. As a control, neutral cues (horizontal arrow) and neutral pictures were presented. The instruction for upwards-pointing arrows was to build up attention for the perception of an emotionally salient picture [23]. The contrast ‘cued versus uncued emotional picture viewing’ was used to study modulation of emotional picture processing by preceding attention. Emotionally salient pictures comprised positive and negative pictures (50% each). The emotional expectancy cue, however, did not distinguish between positive and negative valences in order to avoid valence-specific conditioning effects [5,6].

Thirty-two trials per condition were presented over 4 runs (pseudorandomized and counterbalanced). Between cued and uncued conditions, pictures were matched for valence and arousal. Novel matched pictures were presented at t2.

Subjects were instructed to promptly press a button with each photograph. The button response did not require a specific judgment. Due to technical problems, response times could not be recorded in five healthy subjects. Response times were analyzed using a mixed ANOVA with the between-subjects factor group (healthy, depressed) and the within-subjects factor valence (positive, negative, neutral).

MR images were acquired on a 1.5-Tesla GE Signa whole-body scanner. A total of 251 sequential echo planar functional images were acquired. A total of 251 sequential echo planar functional images sensitive to BOLD contrast were acquired (23 slices with 3.125 mm in-plane resolution, 5 mm thickness, 1 mm gap; T2* weighted gradient echo sequence: TR 2 s, TE 40 ms).

Image processing was performed using SPM2 (Wellcome Department of Imaging Neuroscience, London). Each set of functional volumes was realigned to the first image, mean-adjusted by proportional scaling, resliced and normalized into standard stereotactic space (resulting in an isotropic 3 mm resolution), spatially smoothed with a Gaussian kernel of 8 mm (full-width half-maximum) and high-pass filtered (128 s).

Stimulus and subject effects were estimated using general linear model approach. The stimulus functions were convolved with a hemodynamic response function as implemented in SPM2 to generate the regressors of interest. In a first model, six conditions were modeled, including emotional and neutral picture perception with and without preceding expectancy, respectively, as well as the emotional and neutral expectancy periods preceding the picture perception. In a second valence-oriented model, positive and negative picture perception periods were modeled separately, resulting in eight conditions. Though not involved in the analyses of this study, the two expectancy periods were modeled to reduce the possible confound of picture period by preceding expectancy-related BOLD responses. For second-level random-effects analysis, single-subject contrasts were entered into one-sample and two-sample t-tests across subjects. Responses were considered significant at \( p \leq 0.001 \), uncorrected (corresponding to a t score \( > 3.35 \)), if predicted in our hypothesis concerning the prefrontal cortex. For exploratory purposes, Table 2 also reports activations outside the prefrontal cortex at the same threshold.

Analyses focused on the contrast ‘cued > uncued emotional picture perception’. First, statistical parametric maps were estimated for this and the reverse contrast in the healthy group (one-sample t-test). Then, effects were compared between healthy and depressed subjects (two-sample t-test). To characterize the pattern of prefrontal activation across conditions and groups, parameter estimates were extracted from the prefrontal peak voxels (over smoothed volumes) identified in the group comparison.

To explore effects of emotional expectancy on emotional picture processing in the remitted group, parameter estimates were extracted also for this group from the peak voxels mentioned above. This preliminary analysis served to visualize the activation pattern across conditions in the remitted group.

### Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>HDRS</th>
<th>Duration</th>
<th>Episodes</th>
<th>Hospit.</th>
<th>Medication status</th>
<th>DMPC</th>
<th>DLPC</th>
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<tr>
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<td>26</td>
<td>2</td>
<td>2</td>
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<td>0.22</td>
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<tr>
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<td>26</td>
<td>26</td>
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<td>2</td>
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</tr>
<tr>
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<td>10</td>
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<td>0.63</td>
</tr>
<tr>
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<td>25</td>
<td>2</td>
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<td>1</td>
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<td>F</td>
<td>42</td>
<td>22</td>
<td>5</td>
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<tr>
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</table>

DMPC: dorsomedial prefrontal cortex, DLPC: dorsolateral prefrontal cortex, HDRS: Hamilton Depression Rating Scale, Hospit.: number of hospitalizations (including the present), M: male, F: female, S.D.: standard deviation. Episodes refer to the number of depressive episodes (including the present). Age and duration of illness are reported in years. Medication status refers to the time of the (first) fMRI session (t1). Expectancy effects in the DMPC and DLPC represent the contrasts of parameter estimates for ‘cued > uncued emotional picture perception’; values were multiplied by ten and refer to the peak voxels over smoothed volumes identified in the group comparisons (cf. Figs. 1 and 2 and Table 2).
To explore effects of expectancy during the actual expectancy period, we compared the contrast ‘emotional > neutral expectancy’ between healthy subjects and depressed patients (SPM two-sample t-test).

Response times showed a significant main effect for the factor expectancy ($F_{1,29} = 22.4, p < 0.001$), with faster responses in cued conditions (0.80 ± 0.24, mean ± S.D.) compared to uncued conditions (9.89 ± 0.22). By contrast, there was no significant effect for the factors valence and group as well as for the interaction between expectancy and group and the interaction between valence and group.

In healthy subjects, the contrast ‘cued > uncued emotional picture perception’ revealed a robust BOLD activation in the bilateral DMPFC (bilateral superior, medial and middle frontal gyrus, BA 8/9/10, peak at x = −9, y = 51, z = 42; $t = 7.33$, cluster size = 478). This result replicates our previous findings in a different sample of healthy subjects [5]. The reverse contrast (‘uncued > cued emotional perception’) produced bilateral activation in the posterior dorsolateral prefrontal cortex (DLPFC; inferior frontal gyrus, BA 9/46, peaks at x = 45, y = 3, z = 27; $t = 6.66$, cluster size = 65; and at x = −42, y = 0, z = 33; $t = 6.88$, cluster size = 60).

We next studied the contrast ‘cued > uncued emotional picture perception’ for the comparison ‘healthy subjects > depressed patients’. This analysis revealed effects in the left DMPFC (Table 2, Fig. 1A). Fig. 1B illustrates that healthy subjects showed increased activation in the cued compared to the uncued condition, while no such expectancy effect was present in depression.

The reverse comparison (‘depressed patients > healthy subjects’) revealed effects in the right posterior DLPFC (Table 2, Fig. 2A). When the significance threshold was tentatively lowered to $p < 0.01$, uncorrected, effects were also observed in the left DLPFC suggesting that group differences were not strictly confined to the right hemisphere. Fig. 2B illustrates that healthy subjects showed higher signal intensities during uncued compared to cued emotional picture perception, whereas such difference was not present in depression.

Expectancy-related modulation of emotional picture processing may be influenced by sex, age, illness severity, duration of illness, number of depressive episodes, and number of hospitalizations (Table 1). To explore the relationship between these variables and expectancy effects in the depression group, we tentatively tested for correlation between expectancy effects (in the DMPFC and DLPFC) and each of these variables. These tests revealed no significant correlation (in particular, correlation of expectancy effect in DMPFC with age: Pearson $r = -0.17$, $p = 0.55$; correlation of expectancy effect in DLPFC with age: Pearson $r = 0.28$, $p = 0.32$). These exploratory analyses have to be interpreted with caution, because they are likely underpowered.

Although the emotional expectancy cue did not distinguish between positive and negative valences in our paradigm, we were able to model positive and negative picture periods separately. This allowed studying expectancy effects for positive and negative picture conditions separately. Figs. 1C and 2C illustrate that group differences (Fig. 1A,B and Fig. 2A,B) were more pronounced in the positive picture condition.

To study effects of emotional expectancy during the actual expectancy period, we compared the contrast ‘emotional > neutral expectancy’ between healthy and depressed subjects. This analysis revealed increased activation in the left ventrolateral prefrontal and lateral orbitofrontal cortex in depressed compared to healthy subjects (Table 2).

To explore effects of expectancy on emotional picture processing in the remitted subgroup, parameter estimates were extracted for all conditions from the prefrontal peak voxels identified above in the group comparisons. This analysis showed that, after remission,
the activation pattern tended to normalize in the DMPFC, in particular in the positive picture condition (Fig. 1C). In the DLPFC, by contrast, we did not observe normalization in the positive picture condition (Fig. 2C).

Our data suggest attenuation of expectancy-related prefrontal modulation of emotional picture processing in major depression. Few studies to date have studied emotion modulation in depression. They also suggest prefrontal dysregulation: in a reappraisal paradigm for fMRI [4], the degree of difficulty to down-regulate sadness was correlated with DMPFC activity in both healthy and depressed individuals. Another reappraisal paradigm [15] found greater right DLPFC activation in passive picture viewing versus reappraisal in healthy compared to depressed individuals. Finally, Grimm et al. [12] observed that the impact of judgment expectancy on emotional judgment differed between depressed and healthy individuals in the right DLPFC. Our data extend these studies in four regards: first, using an emotional expectancy paradigm, our study avoids varying explicit task demands during picture presentation. Second, our findings link dorsal prefrontal dysfunction to alterations in expectancy-related modulation of emotional stimulus processing. Third, alterations in DMPFC and DLPFC function particularly concern the positive picture condition. Fourth, the alterations observed seem to disappear with remission of symptoms in the DMPFC, but not DLPFC.

While multiple pathways for emotion regulation have been suggested [20,27], the assumption underlying the present paradigm was that emotional expectancy may enhance the attention directed towards the emotional content of the subsequent picture [23]. Cued and uncued emotional picture conditions only differed in the period preceding the picture perception, but not the picture period itself. In this way, the paradigm allowed studying emotional picture processing and its attentional modulation unaffected of interfering cognitive task demands.

Our expectancy-paradigm revealed altered modulation of DMPFC and posterior DLPFC activity in depressed patients during emotional picture perception. This is in accordance with earlier neuroimaging studies implicating the DMPFC and DLPFC in the pathophysiology of major depression [21,24]. Analysis of the expectancy period of the paradigm revealed enhanced activation in the ventrolateral prefrontal cortex extending to the lateral orbitofrontal cortex in depressed versus healthy individuals. This finding is in accordance with neuroimaging studies in depression reporting increased activation in (ventro)lateral prefrontal regions.

Fig. 1. Healthy individuals > Depressed patients. (A) The comparison ‘healthy controls > depressed patients’ performed for the contrast ‘cued>uncued emotional picture perception’. R, right. (B) Parameter estimates obtained in the DMPFC during cued and uncued emotional picture perception. Error bars show the standard error of the mean. *t = 6.5, p < 0.001; ”t = 2.4, P = 0.07 (2-tailed t-tests). (C) Expectancy-related modulation effect in the DMPFC during positive, negative, and neutral picture perception (contrasts of parameter estimates for cued versus uncued conditions). Error bars show the standard error of the mean. ”t = 3.7, p = 0.001; “t = 2.9, p = 0.007; ”t = –3.0, p = 0.01 (two-tailed t-tests).
during anticipation of reward [10,22] and pain [26]. Our finding suggests that, in depression, different subregions within the prefrontal cortex show alterations at distinct stages of expectancy-induced modulation of emotional stimulus processing. Ventrolateral areas seem to be affected during the expectancy period and dorsal areas during the actual stimulus presentation.

Depressed patients showed attenuated modulation of emotional picture processing particularly in the positive picture condition. This is in accordance with neuropsychological and neuroimaging findings showing blunted responses to positive emotional contents in depression [18]. The observed alteration may contribute to anhedonia and persistent negative mood states [18,21].

Given the negative processing bias in depression [18], one might have anticipated increased modulation of negative stimulus processing in our study. However, our data rather suggest attenuated modulation also in the negative condition, although this effect did not reach significance and was less pronounced than in the positive condition. Our finding is in accordance with a recent meta-analysis [7] demonstrating reduced emotional reactivity to both positive and negative stimuli, with the reduction larger for positive stimuli. Constantly occupied with negative contents, depressed patients may not be able to further increase their attention to negative stimuli in our paradigm.

Because the sample size was small (n = 5) and practice effects cannot be excluded, our exploratory analysis in remitted patients has to be interpreted with caution. One may tentatively suggest that expectancy-related modulation of DMPFC activity may normalize with remission of symptoms, in particular in the positive picture condition. This finding is in line with fMRI studies showing normalization of DMPFC function with remission [16,19]. In contrast to the DMPFC, attenuated modulation of positive picture processing seemed to persist in the DLPFC, which is in accordance with reports of persisting cognitive deficits in euthymic patients [3] and neuropathological alterations in the DLPFC [24].

The present study has preliminary character due to a number of limitations. A relatively liberal significance threshold of \( p < 0.001 \) (uncorrected) in a priori regions of interest was accepted. Furthermore, all but one depressed patient received antidepressant medication and depressed patients were older than healthy individuals. We cannot exclude that medication and age effects account for part of the differences observed between depressed and healthy individuals, given that medication [9] and age [8,11,13,25] can affect attentional and emotional function. However, normalization of DMPFC function was found after remission, when patients were still taking antidepressant medication. In addition, selective serotonin reuptake inhibitors were reported to enhance rather than attenuate responses to emotional stimuli in some brain regions in healthy volunteers [2]. Finally, we observed altered modulation particularly in the positive picture condition. It seems unlikely that this could be due to non-specific medication or age effects. Nonetheless, further

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Depressed patients > Healthy individuals. (A) The comparison 'depressed patients > healthy controls' performed for the contrast 'cued > uncued emotional picture perception'. R, right. (B) Parameter estimates obtained in the DLPFC during cued and uncued emotional picture perception. Error bars show the standard error of the mean. *\( t = -6.7, p < 0.001 \) (two-tailed t-tests). (C) Expectancy-related modulation effect in the DLPFC during positive, negative, and neutral picture perception (contrasts of parameter estimates for cued versus uncued conditions). Error bars show the standard error of the mean. *\( t = -3.2, p = 0.003 \) (two-tailed t-tests).
studies are needed to investigate unmedicated patients and explore the impact of antidepressant medication on BOLD responses.

Another potential limitation concerns distractibility and impaired attention which are common cognitive deficits in major depression. However, they cannot explain our main findings because response times measured during fMRI did not significantly differ between depressed and healthy individuals.

A final limitation is that our expectancy paradigm did not involve behavioral or physiological measures suitable to study the modulation of emotional responses.

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