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Research Report

How do we modulate our emotions? Parametric fMRI reveals cortical midline structures as regions specifically involved in the processing of emotional valences

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Abstract

One of the major problems in affective neuroscience of healthy subjects as well as of patients with emotional dysfunctions is to disentangle emotional core functions and non-emotional processes. Emotional valence is considered an emotional key process. The present study employed a parametric functional magnetic resonance imaging (fMRI) study to address this question. Thirteen healthy volunteers were scanned during emotional stimulus processing (International Affective Picture System). The presented pictures covered the entire range of emotional valences. The fMRI data were consecutively subjected to a preliminary categorical (valence-independent) and a detailed parametric analysis, the latter using individual valence ratings as regressor. The parametric analysis revealed a linear valence-dependent modulation of the BOLD signal in the orbito- and dorsomedial prefrontal cortex (OMPFC, DMPFC), medial parietal cortex (MPC), and insula. In addition, we observed that emotional valence exerts its effects predominantly via modulation of signal decreases. We conclude that the psychological concept of emotional valence may be related to neural processing in cortical midline regions.

Theme: Neural basis of behavior
Topic: Motivation and emotion

Keywords: Emotion; Valence; Cortical midline region; Baseline; IAPS

1. Introduction

One of the most pertinent questions in affective neuroscience of healthy subjects as well as of patients with disturbed emotional processing is how specialized functions for emotional operations can be associated with specific brain regions. Besides genuine emotional factors, accompanying factors are unavoidably involved in emotional tasks. These concern, for example, the induction method as well as cognitive functions such as attention, working memory, and evaluation. Since these accompanying factors are difficult to control for, emotional factors of interest may potentially remain masked. In order to isolate emotional functions from rather accidental accompanying non-emotional processes, tasks are needed which exclusively vary emotional attributes of the presented stimuli leaving all the confounding factors of the task as unaltered as possible. In this study, we propose a parametric design, which uses valence modification of emotional stimuli to modulate exclusively regions involved in a core feature of emotional processing, the attribution of emotional valences.

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Since its photographs are validated according to their emotional valence, the International Affective Picture system (IAPS) [33] was considered as the appropriate tool for this investigation. In this system, emotional valence comprises the continuum between negatively and positively rated emotions on a scale from 1–9. The values 1–3 are ascribed to negative, 4–6 to neutral, and 7–9 to positive valences. Numerous previous neuroimaging studies have used IAPS pictures to investigate the neural correlates of emotional processing. No study has up to now used IAPS pictures for parametric analysis of valence processing. However, several IAPS studies employed categorical analyses to investigate valence processing. Contrasting negative, positive, and neutral pictures against each other, these investigations aimed at identifying regions specifically associated with negative or positive valence [29,30,36,44,49,60]. Cortical regions associated with negative emotions include the amygdala, hippocampus, parahippocampal gyrus, occipitotemporal cortex, right caudate, and cerebellum. In contrast, positive emotions were characterized by activation in the dorsolateral prefrontal cortex, left superior temporal cortex, left caudate, putamen, and striatum. In addition, hemispheric asymmetry has previously been suggested. Positive emotions tend to be lateralized towards the left hemisphere, whereas negative emotions have been associated with the right hemisphere mainly [10,12]. However, a substantial overlap between regions involved in positive and negative emotional processing has also been reported. This overlaps concerns besides subcortical regions (e.g., thalamus, hypothalamus, midbrain) especially the orbitomedial prefrontal cortex (OMPFC) [30,31].

The OMPFC seems to play a central role in emotional processing [12,29,50]. A meta-analysis reviewing 55 neuroimaging studies [50] found the OMPFC involved in a variety of emotional paradigms concerning all kinds of emotions such as sadness, happiness, disgust, and fear [10,15,20,22,49,60]. OMPFC involvement is commonly observed during the induction of emotions in different sensory modalities, including visual, auditory, and gustatory [6,29,41,44–47,55,59]. Additionally, various methods of induction of emotional experience (verbal and non-verbal; current external events and recall of past events) lead to involvement of the OMPFC [17,20,24,25,29,52]. It has therefore been suggested that the OMPFC might be implicated in processes that are common to various emotional tasks such as the experiential aspect of emotional processing, emotional regulation, or emotion-driven decision making.

Given this general function of the OMPFC in emotional processing and its engagement in both negative and positive emotional processing, may we assume that neural activation in the OMPFC is independent of the valence of the presented emotional stimulus? A few studies have reported differences in OMPFC activity associated with the processing of positive, neutral, and negative valences [5,20,29,30,36,49,56,60]. Specifically, when contrasting positively to negatively valenced stimuli, they observed signal increases in the OMPFC. Using olfactory stimuli, a recent study by [5] demonstrated valence-dependent modulation of neural activity in the posteromedial orbitofrontal cortex. They observed that the two odors citral and valeric acid are associated with signal changes in the posteromedial orbitofrontal cortex. These signal changes correlated with the evaluation of the pleasantness of the stimuli: The more positive the stimuli were rated, the higher signal intensity was detected in the posteromedial orbitofrontal cortex.

While this was demonstrated for the olfactory system, valence-dependence has not been investigated yet in the case of visual emotional processing. The difference in modality might be crucial. Psychologically, the visual presentation of emotional photographs from the IAPS might contain a richer semantic content than olfactory stimuli. In addition, different modalities might involve distinct neuronal systems in emotional processing. For example, visual emotional stimuli were found to preferentially activate the amygdala and the visual cortex compared to non-visual induction methods [50].

The aim of the present study was to investigate valence processing in the visual modality. Based on abovementioned findings, we expected involvement of the OMPFC in the modulation of emotional valence. Analogously to the results obtained in the OMPFC with olfactory stimuli, we assumed valence-dependent continuous signal changes in the OMPFC. The psychological continuum of emotional valences, as presupposed in the IAPS, should then be mirrored in an analogous continuum of physiological signal changes in the OMPFC. In order to test this hypothesis of continuous valence-dependent signal changes in the OMPFC, we performed a parametric analysis of data acquired in fMRI during visual presentation of emotional stimuli from the IAPS.

2. Methods

2.1. Subjects

We studied 13 healthy subjects (3 women, 10 men; average age: 27.0; range: 23 years to 34 years). They all had at least 16 years of education with achievement of a college degree. The subjects were thoroughly questioned about psychiatric, neurological, or medical diseases as well as the use of psychoactive substances by a psychiatrist (GN) using a custom-made semistructured clinical questionnaire. None of the subjects included in the study had history of axis I disorder, neurological, or severe medical illness. All subjects denied recent substance abuses. All subjects were right-handed as assessed by the Edinburgh Inventory for Handedness. After detailed explanation of the study design and potential risks, all subjects gave written informed consent.

The same sample has also been used in a previous study by Northoff et al. [45] which had focused on the judgment period of the paradigm, whereas the present study analyzes the period of picture presentation.

2.2. Paradigm

Emotional stimulation was induced by the presentation of standardized pictures taken from the IAPS that covered the entire range of emotional valences. Based on large-sample valence rating studies, a rank between 1 and 9 had been assigned to each of these pictures according to their valence [11]. Negative (valence scores 1–3), neutral (valence scores 4–6), and positive (valence scores 7–9) IAPS pictures covering the entire range of valences from 1 to 9 were selected for presentation. Pictures were presented for a duration of 2 s. Picture sets were counterbalanced across subjects as well as within each subject. To exclude a systematic correlation, semantic contents were adjusted across pictures of different valence. Therefore, the three groups (i.e., neutral, positive, and negative pictures) contained similar numbers of pictures showing people, faces, animals, objects, and scenes.

IAPS picture viewing was followed by a judgment task related to the preceding picture. The judgment had to be given within 2 s. To exclude fixed expectation effects during the viewing of the IAPS pictures, the paradigm included two types of judgment tasks: emotional and non-emotional judgment tasks. The emotional judgment tasks consisted in a positive/negative (P/N) judgment and a feeling/absent feeling (F/A) judgment. The non-emotional judgment task consisted in a vertical/horizontal (V/H) judgment, reflecting a spatial judgment. In this task, subjects were required to indicate if the orientation of the previously presented IAPS pictures has been portrait or landscape format. The type of judgment to be given was indicated by appearance of the respective letters (P/N, F/A, or V/H) on the screen, which were presented in randomized order. In this way, we tried to ensure that the subjects did not only focus on one aspect of the pictures during emotional stimulus processing. In addition, the unpredictability of the judgment increased the level of attention during the task. Since we applied two types of emotional judgment and only one type of non-emotional judgment, the judgment tasks are not equally matched. However, the judgment periods were always following the period of emotional stimulus processing which is the focus of the present analysis. During emotional picture presentation, the subjects did not yet know which type of task would follow. Therefore, we do not expect significant influence of this mismatch on our results.

Finally, judgments served for behavioral validation of effects of IAPS pictures on subjective experience within the scanner while they were not used for analysis. The response was made by pressing different buttons with the right thumb for P/F/V and the left thumb for N/A/H. Reaction times were measured.

Following the IAPS picture (2 s) and the judgment screen (2 s), a fixation cross appeared consisting of a horizontal and a vertical bar in low colors (black, brown). This picture served as baseline condition [43,57]. The duration of the baseline condition was randomly varied between 4 and 8 s (4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0 s) accounting for variable stimulus onset asynchrony. A total of 280 events (each including IAPS picture presentation, judgment task and fixation cross) were presented in four runs. The different types of IAPS pictures and judgment tasks were equally distributed over the four runs. Order of IAPS pictures as well as of judgment tasks was randomized. The only restriction to pure random order was to avoid to show more than two IAPS pictures of the same type (e.g., three negative pictures) consecutively. Accordingly, during the presentation of an IAPS picture, subjects did not know what type of judgment had to be given subsequently.

Prior to the experimental session, subjects were familiarized with the paradigm by completing a test run consisting of 20 IAPS pictures and judgment tasks.

In fMRI, pictures were automatically projected via a forward projection system on a screen at the end of a patient gurney. Subjects lay supine in the scanner and viewed the screen through a mirror positioned on the head coil. The subjects were asked to keep their eyes open and to fixate the middle of the screen. They were asked to move neither finger, head nor body during the presentation of pictures.

2.3. Behavioral monitoring

Reaction times were defined as the time between the onset of the judgment screen and the subsequent button press. To test for differences concerning the reaction times, a two-way repeated measurements ANOVA with the factors ‘judgment’ (emotional, non-emotional) and ‘emotional valence’ (positive, negative, neutral) was performed.

Subjects were asked to assess valence, dominance, and arousal of IAPS pictures in an additional session (following fMRI). For this purpose, the self-assessment manikin (SAM) was used [33]. The subjects were instructed to rate the pictures as close as possible to the way they experienced them in the scanner. The presentation was self-paced, thus the subjects could decide themselves how much time they need to perform the ratings. By this means we verified that our subjects reacted in the same way to the pictures as the representative group tested by [33]. The valence ratings were subsequently used for parametric analysis of fMRI data. The judgments made during fMRI scanning were compared with the values obtained in the post hoc assessment (SAM). To compare the post hoc SAM ratings with the subjective ratings during the fMRI-scanning, we performed a Pearsons correlation. The comparison has been conducted between the results of the positive/negative judgments and the valence ratings of the SAM as well as between the feeling/absent feeling

judgments and the valence ratings of the SAM. To that end, the on-line ratings of the positive/negative judgments and the feeling/absent feeling judgments were attributed to the valence values. For the positive/negative judgments, valences <5 were assigned to negative judgments and valences >5 to positive judgments. For the feeling/absent feeling judgments, valences from 4–6 were assigned to absent feeling judgments and valences from 1–3 as well as from 7–9 to feeling judgments.

Psychological state before and after fMRI was investigated with the STAI (State Anxiety Inventory) using paired *t* tests. By this means we wanted to ensure that the general emotional state was the same across the experiment.

2.4. fMRI scanning procedures and image analyses

Scanning was performed on a 1.5 T Siemens Vision (Erlangen, Germany) at the Beth Israel Deaconess Medical Center, Boston, USA. A gradient-echo T2*-weighted echo-planar MR sequence was used for fMRI with the following parameters: TE (echo time) = 50 ms, FOV (field of view) = 240 cm, matrix = 64 × 64 interpolated to 128 × 128, voxel size: 4 × 4 × 6 mm^3. Using a midsaggital scout image, we acquired 18 contiguous axial slices parallel to the anterior–posterior commissure (AC–PC) plane covering the entire brain in less than 2 s. The first three acquisitions were discarded due to T1-saturation effects. Prior to the functional MR sequence, an anatomical data set was acquired by using a T1-weighted gradient echo pulse sequence with the following parameters: FOV = 256 cm, matrix = 256 × 256, voxel size = 1 mm^3.

Image processing and statistical analyses were carried out using SPM99 (Statistical Parametric Mapping, Wellcome Institute of Cognitive Neurology, London, UK). All volumes were realigned to the first volume, corrected for motion artifacts, mean-adjusted by proportional scaling, co-registered with the subject's corresponding anatomical (T1-weighted) image, resliced, and normalized (2 mm^3) into standard stereotactic space (template provided by the Montreal Neurological Institute), and smoothed using an 8-mm full-width-at-half-maximum Gaussian kernel. In addition, the time series of hemodynamic responses were high-pass filtered to eliminate low-frequency components, temporarily smoothed, and adjusted for systematic differences across trials. These adjusted measures were subjected to the statistical analyses. Voxel associated with movement conditions was searched for by using the General Linear Model approach for time-series data [18]. The anatomic localization of local maxima was assessed by reference to the MNI brain as provided by SPM. The stereotactic coordinates of the voxel of local maximum significant activation were determined within regions of significant activity change.

The image analysis was performed by using a general linear model for event-related designs [26]. The presentation of each IAPS picture as well as of each judgment has been modeled at each event onset by using a synthetic hemodynamic response function and its temporal derivative. Two types of statistical analyses of the fMRI data were performed. In a first step, we adopted a categorical analysis. The constructed regressors were the presented pictures, irrespective of their emotional valence. Thereby, the difference between IAPS picture viewing and baseline condition was modeled [43,57]. The main purpose of this analysis was to detect the regions responsible for neural processing during the presentation of the IAPS pictures in general.

In a second step, we adopted a parametric analysis [8] using the valence ratings (1–9) as modulation parameter. As in the first step, it was tested against baseline. The valence values used for this analysis were taken from the SAM ratings of our subjects. This was to assure that the appropriate (i.e., individually rated) valence values were applied to the analysis for each subject.

The analysis tested for a linear relationship between regional signal changes and valences of IAPS pictures and thus valence-dependent modulation of signal intensity in particular regions.

The linear relationship of the changes in the BOLD signal with the valence values was further illustrated by showing the regressions for local maxima of the BOLD signal from the parametric analysis.

Though not involved in the baseline comparisons and parametric analysis of this study, the different judgment periods were modeled as separate conditions (effects of no interest) to reduce the possible confound of the emotional stimulus processing by subsequent judgment-related BOLD responses. The type of judgment required after the periods of emotional stimulus processing was randomized across the experiment. Thus, during emotional stimulus processing, the subjects were unable to predict which kind of judgment task would follow.

For the fMRI group analyses, all images of all subjects were analyzed in one design matrix, generating a random-effects model, allowing inference to the general population. Due to our a priori hypothesis-driven approach, we set the level of significant regional activity changes to $Z > 3.29$ ($P < 0.001$, uncorrected, voxel level) thereby achieving a high level of sensitivity for detection of both signal increases and signal decreases [14,21,22].

To control for possible confound of valence with arousal, we performed a parametric analysis analogous to the valence analysis by using the arousal ratings as modulation parameter. By this means we tested for a linear relationship between regional signal changes and arousal scores of IAPS pictures (i.e., arousal-dependent modulation of signal intensity).

Additionally, to explore potential gender effects, we performed the categorical as well as the parametric analyses separately for the group of the male and the female subjects. The results of these analyses were then compared between the groups using two sample *t* tests.

3. Results

3.1. Behavioral results

The two-way repeated measurement ANOVA revealed no significant differences concerning the reaction times for the factor judgment and valence and the interaction of both factors (all $P > 0.05$).

The valence ratings (1–9) of our sample revealed a mean of 2.19 (SD ±0.7) for negative pictures, a mean of 4.94 (±1.3) for neutral pictures, and a mean of 7.14 (±1.8) for positive pictures. The correlation coefficients between the self-reported scores of our sample and the sample of Lang et al. [33] were 0.71 for negative pictures, 0.83 for neutral pictures, and 0.79 for positive pictures thereby showing a significant correlation for all of the three dimensions ($P < 0.05$). We found significant positive correlations between the post hoc SAM ratings and the ratings performed during the fMRI-scanning ($r = 0.70$, $P < 0.05$, positive/negative judgments; $r = 0.64$, $P < 0.05$, feeling/absent feeling judgments). This supports that the post hoc SAM ratings reflect the experiences of the subjects during the scanning. The State Anxiety Inventory revealed no significant differences between the two time points before and after the fMRI experiment.

3.2. fMRI results

The first step of analysis (categorical) revealed multiple significant foci of signal change in the comparison of IAPS picture viewing with our baseline condition. Significant signal changes were observed in cortical midline regions such as the OMPFC ($x = -2$, $y = 54$, $z = 14$; $Z = 3.65$) and the DMPFC ($x = 4$, $y = 48$, $z = 40$; $Z = 3.68$) (Table 1). Moreover, significant signal increases were observed in the bilateral posterior parietal cortex ($x = -48$, $y = -67$, $z = 28$; $Z = 3.36$) ($x = 50$, $y = -63$, $z = 25$; $Z = 3.34$), the posterior cingulate ($x = 0$, $y = -38$, $z = 40$; $Z = 3.83$), and the thalamus/hypothalamus ($x = 0$, $y = -8$, $z = 4$; $Z = 3.39$) (Table 1, left part).

The second step of analysis tested for a positive correlation between the changes of the valence and the linear change of the BOLD signal. It revealed valence-dependent modulation of signal intensity in the OMPFC ($x = 16$, $y = 56$, $z = 19$; $Z = 3.35$; close to the pregenual anterior cingulate) and the DMPFC ($x = 12$, $y = 48$, $z = 24$; $Z = 3.29$). Other regions showing valence-dependent modulation included signal increases in the MPC ($x = -2$, $y = -34$, $z = 60$; $Z = 3.68$) and the left insula ($x = -54$, $y = -10$, $z = 14$; $Z = 4.32$). It should be noted that both comparisons overlap with regard to the involvement of the OMPFC and DMPFC. The other regions, in contrast, were either involved in non-valence-dependent or valence-dependent signal changes. The posterior cingulate showed signal changes only in the categorical analysis, whereas involvement of the medial parietal cortex was revealed only in the parametric analysis (Table 1 and Fig. 1, upper part).

Table 1
Signal changes induced by IAPS picture viewing independent from and dependent on emotional valence

	Signal changes associated with IAPS stimulus processing	Signal changes due to parametric modulation by valence
Orbitomedial prefrontal cortex (OMPFC)	−2/54/14, 3.65	16/56/19, 3.35
Dorsomedial prefrontal cortex (DMPFC)	4/48/40, 3.68	12/48/24, 3.29
Medial parietal cortex (MPC)	–	−2/−34/60, 3.68
Insula	–	−54/−10/14, 4.32
Bilateral posterior parietal cortex	−48/−67/28, 3.36; 50/−63/25, 3.34	–
Thalamus/hypothalamus	0/−8/4, 3.39	–
Posterior cingulate	0/−38/40, 3.83	–

x, y, z: MNI coordinates in mm. x describes right (+)/left (−), y anterior (+)/posterior (−), and z superior (+)/inferior (−) distances (e.g., 21/23/43, 3.45 ≅ $x = 21/y = 23/z = 43$, $Z = 3.45$). Coordinates of the local maxima of regional signal increases are given. Z = Z-score. Only signal increases with $Z > 3.29$ ($P < 0.001$, uncorrected, voxel level) are described. Signal changes associated with IAPS picture viewing reflect the comparison between the IAPS picture presentation condition and the baseline condition independent from the valence of the pictures (left column). In contrast, the parametric analysis tested for a linear relationship between regional changes in the BOLD signal and valence of the presented IAPS pictures. The IAPS pictures were modeled as a regressor according to their valence ranging from 1 to 9. The parametric signal changes were tested against the baseline condition. Regions are listed that show a positive linear relationship between valence and BOLD signal changes (right column). Note the overlap between both comparisons with regard to involvement of OMPFC and DMPFC. The other regions, in contrast, were either involved in emotional stimulus processing or valence-dependent modulation.

As depicted in Fig. 1, OMPFC, DMPFC, and MPC showed a linear relationship between the valence of the IAPS picture and the BOLD signal change relative to baseline. Valence-dependent modulation was exerted predominantly via modulation of signal decreases in all three regions. All three regions showed significant deactivation associated with negative valences. The lower (i.e., more negative) the valence of an IAPS picture was rated, the larger was the signal decrease detected in OMPFC, DMPFC, and MPC. Increasing valence scores (more positive stimuli) were associated with less deactivation. Neutral valences, representing the intermediate range of the valence scale, revealed signal intensities that lay between the intensities of negative and positive valences. Positive valences were associated with higher signal intensities in all three regions compared to negative and neutral valences. Yet, positive valences were still associated with signal decreases compared to the resting baseline in DMPFC and MPC. In contrast, the OMPFC showed signal increases relative to baseline during positive valences.

The parametric analyses did not show significant negative correlations ($P < 0.001$, uncorrected).

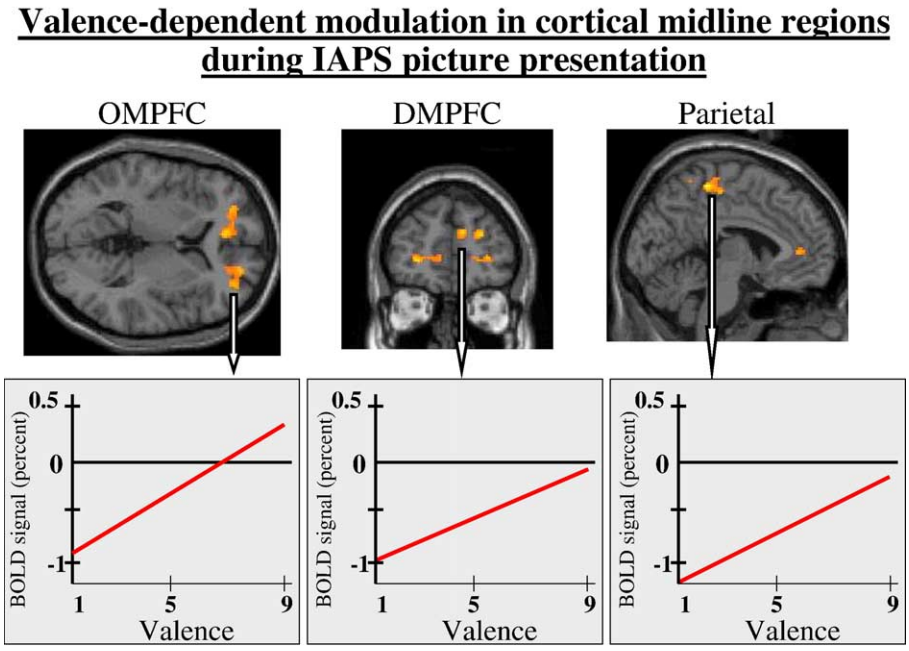

Fig. 1. Upper part: fMRI images represent results from a random-effects group analysis ($n = 13$) depicted on a standard MNI brain. x, y, z: MNI coordinates in mm. x describes right (+)/left (−), y anterior (+)/posterior (−), and z superior (+)/inferior (−) distances. Z = Z-score. Only regions with $Z > 3.29$ ($P < 0.001$, uncorrected, voxel level) are described. The aim of the analysis was to characterize the valence-dependent modulation of the BOLD-signal during the presentation of IAPS-pictures. To that end, we adopted a parametric analysis using the valence ratings (1–9 rated by the subjects in a post hoc analysis) as the modulation parameter, which was tested against baseline. Valence-dependent modulations of regional signal intensities during presentation of IAPS pictures were obtained in OMPFC ($x = 16$, $y = 56$, $z = 19$; $Z = 3.35$), DMPFC ($x = 12$, $y = 48$, $z = 24$; $Z = 3.29$; visible in the coronal image), MPC ($x = -2$, $y = 34$, $z = 60$; $Z = 3.68$), and left insula ($x = -54$, $y = -10$, $z = 14$; $Z = 4.3$). Lower part: The parametric relationship between picture valence (x-axis, valence values from 1 [negative] to 9 [positive]) and signal percent change (y-axis, intensity change of the BOLD signal) during viewing of IAPS pictures is demonstrated. The regional local maxima of valence-dependent modulation were correlated with the picture valences. Parametric valence-dependent modulation of signal percent change was found in the following regions during IAPS picture viewing: The OMPFC ($x = 16$, $y = 56$, $z = 19$; $Z = 3.35$), the DMPFC ($x = 12$, $y = 48$, $z = 24$; $Z = 3.29$), and the MPC ($x = -2$, $y = -34$, $z = 60$; $Z = 3.68$). OMPFC = orbitomedial prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, MPC = medial parietal cortex.

The parametric analysis using the arousal ratings as modulation parameter revealed no significant arousal-dependent signal modulation ($P < 0.001$, uncorrected) in our regions of interest, such as OMPFC, DMPFC, and MPC. However, a linear correlation with the arousal scores was found in the medial cerebellum. Since we focused our analysis on the valence processing in the cortical midline regions, we did not further pursue this finding.

The comparison between the male and female study groups revealed no significant difference, neither in the categorical nor in the parametric analysis ($P < 0.001$, uncorrected).

4. Discussion

By specifically varying the emotional valence of visual stimuli, we were able to reveal neural correlates of valence processing. We report that the orbitomedial prefrontal cortex (OMPFC), dorsomedial prefrontal cortex (DMPFC), medial parietal cortex (MPC), and insula show valence-dependence during emotional stimulus processing. Moreover, we found that emotional valence exerts its effects predominantly via modulation of signal decreases.

Our results confirm previous studies that have implicated the OMPFC in emotional processing [17,22,24,25,41,50,52]. In accordance with our findings, a few studies have previously suggested a role for the OMPFC in valence processing [20,29,30,36,49,56]. However, these studies focused on categorical comparisons.

Our results demonstrate that signal changes in the OMPFC are linearly dependent on the valence of visual stimuli (Fig. 1). It should be noted that the OMPFC shows a linear rather than a (inverted) U-shaped correlation curve. The latter would have been associated with strong and similar responses to both negative and positive valences as opposed to less signal changes in the intermediate valence range (neutral stimuli). Such a curve would have favored a distinction between emotional and non-emotional processing based on the emotional load of the stimuli. Instead, the continuum of valences ranging from negative over neutral to positive emotions, as presupposed in the International Affective Picture System [33], is reflected in our data by an analogous continuum of signal changes in the OMPFC. Our results thus suggest that Lang's continuum of valences is not only psychologically valid but may also have a physiological basis.

Our finding of a linear correlation between valence and OMPFC activity is consistent with a recent study focusing

on olfaction [5]. Consistent with our results obtained with visual stimuli, a positive correlation was observed between stimulus valence and brain activity in the posteromedial orbitofrontal cortex, posteriorly adjacent to the orbitomedial prefrontal region observed in our experiment. Since similar results were obtained with visual and olfactory stimuli, it might be concluded that coding of valence in the OMPFC is independent of the sensory modality used in the task.

In addition to these consistent findings, they also reported an inverse correlation in the left anterior lateral and the right anterior medial orbital cortex, which was not observed in our experiment. The discrepancy to our findings may be due to differences in the processing of olfactory and visual stimuli [5,23].

Besides the OMPFC, the DMPFC was engaged in valence-dependent modulation. Like the OMPFC, the DMPFC has frequently been associated with emotional processing [50]. However, OMPFC and DMPFC are implicated in different components of emotional processing: While the OMPFC is engaged in various tasks involving stimulus processing of emotional pictures, the DMPFC is predominantly modulated when emotions are evaluated [22,28,32,45]. Similarly, picture rating with regard to pleasantness was associated with DMPFC activation compared to emotional stimulus processing [58]. In our study, OMPFC as well as DMPFC showed valence-dependent modulation. It might thus be speculated that the processing of valence is involved in both emotional stimulus processing and evaluation of emotional processing.

We were also able to identify valence-dependent modulation in the insula and MPC. Interestingly, these two regions showed no signal changes in the categorical analysis, whereas they revealed valence-dependence in the parametric analysis. This underlines the valence-dependence of the signal changes in these regions. Valence-dependent modulation of the insula is in accordance with a recent study [56], which employed gustatory stimuli to investigate valence processing. Consistent with our findings, the anterior ventral insula responded preferentially to pleasant compared to unpleasant taste (see also [29]).

Some investigators hold that the right hemisphere is critically important in the processing of emotions (e.g., [1,7]). With regard to these studies, our observation of valence-dependent modulation in the left insula appears counterintuitive. However, a recent meta-analysis on 106 neuroimaging studies of emotion found no substantial support for the right hemispheric asymmetry hypothesis, since they observed approximately equivalent numbers of left- and right-sided maxima [42]. This is consistent with another meta-analysis on 65 neuroimaging studies of emotion, which equally found no substantial support for the right hemispheric asymmetry [60]. It might be speculated that in addition to emotional processing further factors have to be taken into account to explain the lateralization. According to the above-cited meta-analyses, such factors have not been revealed yet.

A general methodological problem in investigating valence processing is that it may be confounded by other factors such as the processing of semantic content or of arousal. In the present study, visual stimuli were adjusted for semantic contents across valences. Concretely, similar objects were presented in positive, negative, and neutral photographs.

In contrast to semantic contents, arousal is more difficult to control for. In general, negative stimuli are often more arousing than positive, which are, in turn more arousing than neutral stimuli. In the visual modality, this problem can only partially be solved by adjusting photographs for colors, brightness, complexity, and composition, as accomplished in the IAPS [33]. Therefore, the comparison of negative with positive and even more of negative with neutral stimuli may be confounded by differing arousal values.

To control for the influence of arousal, we performed a parametric analysis using the arousal ratings as modulation parameter. We did not find a significant correlation in the OMPFC, the DMPFC and the MPC. It seems therefore unlikely that the observed valence effect in these regions is due to a confounding arousal effect. However, there can still be an effect, which may become visible if bigger samples are investigated. We did not model the arousal ratings as "covarites of no interest" since due to the strong correlation with valence ratings an analysis may lead not only to the reduction of possible influence of arousal, but also of valence itself. Thus, a possible influence of arousal cannot be completely excluded.

However, this seems not to be the case in the findings presented here. We observed a linear correlation between valences and brain activity. This means that the largest differences were detected between negative and positive valences. Neutral valences showed signal changes in the intermediate range between negative and positive valences. Since neutral stimuli are generally less arousing than positive stimuli, it may be concluded that the observed modulation was not due to arousal but rather to valence-dependence. For arousal dependence, one would have expected that the signal changes related to positive valences lie in the intermediate range between negative and neutral valences.

Our conclusion is supported by the abovementioned studies [5,56]. Employing olfactory and gustatory stimuli, they were able to dissociate intensity and valence processing more clearly than possible in the visual modality. Both studies found regions in the orbitofrontal cortex correlated with valence but not arousal. It might thus be suggested that valence coding in the OMPFC is arousal-independent.

Also consistent with our findings, [5,56] did not find valence-dependence in the amygdala. Instead, amygdala activation correlated positively with stimulus arousal. These findings challenge long-held notions regarding amygdaloid representation of negatively valenced stimuli [2,30,50]. Anderson et al. [4] propose that arousal coding in the

amygdala is valence-independent. This assumption is in accordance with findings demonstrating amygdala engagement in the processing of positive stimuli [9,36]. It is also consistent with lesion studies showing that positive and negative affectivity remains intact in amygdala lesions but not in lesions affecting the prefrontal cortices [3,12]. It might be assumed that the high intensity often associated with negative stimuli may have contributed to the view that the amygdala plays a specific role in the processing of negative stimuli. Finally, the differing results in various studies with regard to the amygdala may partly also be due to the comparison of unequal groups. The processing in the amygdala has been demonstrated as different in men and women [54].

The subject sample studied here is characterized by an unequal gender distribution (3 women, 10 men). This makes it difficult in the present study to analyze gender differences which have previously been observed in visual emotion paradigms [53,61]. Tentative gender comparison revealed no significant differences, neither in the categorical nor in the parametric analysis. This finding seems to suggest that gender effects do not play an important role in our paradigm. However, it is acknowledged that our data do not allow to definitely exclude gender differences, given the unequal distribution in our study sample.

Furthermore, it may be argued that the period of emotional stimulus processing has already involved some kind of judgment. The present paradigm does not allow to exclude the possibility that subjects performed (implicit random) judgments, before the actual explicit judgment instruction was given. However, it should be taken into account that we applied three different judgment tasks in unpredictable order after a presentation time of 2 s. It seems unlikely that the subjects implicitly performed all three types of judgment within the 2 s of emotional stimulus presentation. Moreover, the subjects were explicitly requested not to judge before the judgment instruction was signaled.

In contrast to other studies (e.g., [35]), we did not find differences in the reaction times between positive and negative stimuli. This may mainly be due to our restricted sample size. A bigger sample may have revealed such differences.

Furthermore, we used behavioral ratings which were acquired after scanning to simplify the on-line button-press procedure. Although we found a significant correlation with the on-line ratings, the post hoc ratings may only be considered as an index of the on-line experiences. Therefore, we cannot exclude a possible difference of the on-line experience and the post-hoc ratings.

We did not apply methods to recover a possible signal loss in the orbitofrontal cortex. Since it is usually assumed that possible susceptibility artifact leads to a lower signal intensity, it may be concluded that our signal in the OMPFC might be underestimated [13]. However, other influences of possible susceptibility artifacts cannot be excluded.

Our study revealed valence-dependent modulation in regions located in the midline of the cortex. Since OMPFC, DMPFC, and MPC show a similar mode of activation, they might be considered a functional unit. In previous neuroimaging studies, all three regions revealed signal decreases during various experimental tasks relative to a resting baseline [6,16,22,38,40,45,55]. It has therefore been assumed that neural activity in OMPFC, DMPFC, and MPC is predominantly modulated by deactivation [21]. In consistence with these findings, we found that valence processing in OMPFC, DMPFC, and MPC mainly concerned modulation of deactivation. All three regions showed substantial deactivation associated with negative valences, which was for the OMPFC previously reported by [36]. Deactivation attenuated with decreasing negativity of the stimuli. Positive valences revealed higher signal intensities in all three regions compared to negative and neutral valences. Yet, positive valences were still associated with signal decreases compared to the resting baseline in DMPFC and MPC. In contrast, the OMPFC showed signal increases relative to baseline during positive valences. The latter finding is in consistence with the abovementioned study [5]. When comparing negatively and positively valenced olfactory stimuli to a resting baseline (clean air), they detected signal decreases during negative stimuli, whereas positive valences were associated with signal increases.

It should be noted that the exact physiological meaning of signal decreases in fMRI, as distinguished from signal increases, has not yet been elucidated [22,37]. Whether these signal decreases reflect neural inhibition or reduced excitatory input remains unclear. The exact physiological interpretation of the observed signal decreases remains therefore uncertain.

A few studies have previously reported signal increases associated with negative valences in medial prefrontal cortical regions [10,29,30]. At first view, this seems to conflict with the results reported here. However, these studies did not consider a resting baseline condition. Instead, they directly compared emotional stimulation with non-emotional tasks. These control tasks involved cognitive factors like attention, working memory, and judgment. Since demanding cognitive tasks are known to induce significant deactivation in medial prefrontal regions [6,21,22,27,38,40,45,55], strong deactivation in the control tasks might mask deactivation in the main (i.e., emotional) condition. Accordingly, the signal increases observed during emotional stimulation might have been due to less deactivation rather than ‘true’ activation. A distinction between less deactivation and ‘true’ activation can be made only by additional comparisons of both emotional and active control conditions with a resting baseline [22,45,57].

In our study, each trial consisted of three consecutive elements (picture presentation, judgment, baseline) resulting in overlapping BOLD responses between the different periods of a trial. Within the general linear model as used

by SPM99, we separately modeled the periods of picture presentation, judgment, and baseline using canonical hemodynamic response functions (HRF) and their temporal derivatives. By this means we aimed to separate the temporal profile of the hemodynamic response across overlapping trial periods. This has been described for interstimulus intervals, which are not shorter than 2 s as applied in our design [19,39]. However, we cannot exclude that the decorrelation has only been partial. Thus, the baseline period may partly be confounded with the hemodynamic response related to the experience period and the judgment period.

It also seems conceivable that the emotions induced by the pictures might have persisted during the baseline period although the emotional stimuli were no longer present. If one also assumed that the baseline period involved less judgment-related processing than the period of picture presentation, one could conclude that the comparison 'picture presentation > baseline' may subtract out the processing related to experience and reveal the processing related to emotional judgment. Such an interpretation may fit in with the theory of "the default mode of the brain" [21,51]. This theory posits a high baseline activity for the OMPFC, DMPFC, and MPC. Either of the regions exhibits a high level of neural activity during so-called resting conditions such as a fixation task [21,22,38,51]. Together with the lateral parietal areas, they show the highest baseline activity during the resting state. This activity is attenuated during cognitively demanding tasks.

On the basis of this theory, our baseline (fixation task) involving internal emotional experience may be related to the default mode of the brain. Therefore, it comes as no surprise that the highest neural activity was observed during the baseline period in our study. The period of emotional stimulus presentation might contain elements of a goal-directed task (advance judgment). Thus, our results of neural deactivation observed in the cortical midline structures in the comparison between emotional stimulus presentation and baseline seem to be in accordance with the default theory of the brain.

In contrast to our findings, Gusnard et al. [22] found increases in the DMPFC compared to a resting baseline and to a cognitive control. They suggest that such increases occur specifically when attention is directed towards self-referential or introspectively oriented activity. This interpretation is compatible with the finding of signal decreases in our paradigm. In our study, we compared emotional stimulus processing (which requires externally oriented attention and might involve elements of judgment in our paradigm) with baseline (which may involve 'internal' emotional processing). Thus, Gusnard et al. observed signal increases in the DMPFC during an introspectively oriented task, while our paradigm produced decreases during a rather externally oriented task.

It has been assumed that the baseline activity may play a role in the assessment of the salience and behavioral significance of internal and external stimuli [22,51]. Based on our findings, we suggest that valence processing may be considered as an element of this surveillance process. Valence processing seems to be critically involved by guiding efficient behavioral responses to survival-relevant signals. For instance, negatively valenced signals may induce fear and enable an individual to withdraw [34,48]. Conversely, positively valenced stimuli may mobilize an individual to approach. Behaviorally, negative stimuli might be more relevant than positive. Accordingly, it seems plausible that, in this study, negative valences were found to elicit larger modulation of the 'default mode' (i.e., deactivation) than positive valences. Psychologically, the valence-dependent deactivation might thus reflect a reallocation of attentional resources from surveillance to goal-directed behavior. Once an emotional stimulus is detected, neuronal processes involved in goal-directed behavior might supersede those associated with the surveillance function. This might correspond to deactivation in the OMPFC (subserving surveillance) and concurrent activation in lateral cortical regions (subserving goal-directed behavior; [45]).

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