

# Functional Dissociation between Medial and Lateral Prefrontal Cortical Spatiotemporal Activation in Negative and Positive Emotions: A Combined fMRI/MEG Study

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The orbitofrontal cortex has been cytoarchitecturally and connectionally subdivided into a medial and a lateral part which are assumed to subserve distinct functions in emotional processing. However the exact spatiotemporal mechanisms of negative and positive emotional processing in medial and lateral orbitofrontal cortex remain unclear. We therefore investigated spatiotemporal orbitofrontal and prefrontal cortical activation patterns during emotional stimulation in a combined fMRI/MEG study. We investigated 10 healthy subjects, 5 women and 5 men. Positive and negative pictures from the International Affective Picture system (IAPS) were used for emotional stimulation, whereas neutral and gray pictures were taken as control conditions. fMRI/MEG measurements covered the whole frontal lobe and a time window between -2000 and +200 ms around motor responses (right index finger extension) associated with each picture. Positively and negatively correlated activities were determined in various prefrontal/frontal cortical regions in fMRI. Isocontour maps and single dipoles in MEG were analyzed in 50 ms time windows ranging from -2000 to +200 ms. Dipoles and fMR images were mapped on three-dimensional anatomical MRI so that anatomical localization of single dipoles and regional fMRI activity could be compared. Both negative and positive emotional conditions differed from non-emotional control conditions by strong orbitofrontal and lateral prefrontal activation as well as by the presence of early magnetic fields (-1700 to +1100 ms). Negative emotional processing was characterized by strong medial orbitofrontal activation and earlier (-1700 ms), stronger and more medially oriented orbitofrontal dipoles. In contrast positive emotional processing showed a rather strong activation in lateral prefrontal cortex with later (-1500 ms), weaker and more laterally oriented orbito- and prefrontal dipoles. Negative emotional processing can be characterized by strong and early medial orbitofrontal cortical activation, whereas positive emotional processing showed rather later and weaker activation in lateral orbitofrontal/prefrontal cortex. Such a functional dissociation between medial and lateral orbitofrontal/prefrontal cortex during negative and positive emotional processing lends further support to the assumption of a functional subdivision in the orbitofrontal cortex.

## Introduction

The orbitofrontal cortex has been divided into a medial and a lateral part based upon cytoarchitectonic (the medial part is agranular or dysgranular, whereas the lateral part is rather granular) and connectional (the medial part is closely connected to ventrolateral parts of the basal nucleus of the amygdala as well as to the hippocampal formation and the anterior cingulate, whereas the lateral part is related to medial and dorsal parts of the basal nucleus of the amygdala as well as to sensory and premotor areas and the posterior cingulate) differences (Morecraft *et al.*, 1992; Bates and Goldman-Rakic, 1993; Carmichael and Price, 1994, 1995a,b, 1996; Morecraft and Van Hoesen, 1998). Functionally the medial orbitofrontal cortex

seems to be specialized for emotional processing, whereas the lateral orbitofrontal cortex has been related to a more general function of associating emotions with cognition (Baker *et al.*, 1997; Drevets and Raichle 1998). However, the exact role of medial and lateral orbitofrontal cortex in emotional processing, concerning emotional valence (either negative or positive), time course and functional connectivity, remains to be clarified.

Several imaging studies have demonstrated the importance of medial orbitofrontal/prefrontal and lateral orbitofrontal/prefrontal cortex during negative and positive emotional stimulation (Pardo *et al.*, 1993; George *et al.*, 1995; Baker *et al.*, 1997; Irwin *et al.*, 1997; Lane *et al.*, 1997a,b,c; Paradiso *et al.*, 1997; Phillips *et al.*, 1997; Reimann *et al.*, 1997; LaBar *et al.*, 1998; Beauregard *et al.*, 1998; Büchel *et al.*, 1998; Morris *et al.*, 1998). Some authors argue for valence specificity (George *et al.*, 1995; Imaizumi *et al.*, 1997; Irwin *et al.*, 1997; Lane *et al.*, 1997a,b,c; Paradiso *et al.*, 1997; Phillips *et al.*, 1997; Pihan *et al.*, 1997; Aftanas *et al.*, 1998; Lang *et al.*, 1998; Morris *et al.*, 1998), others rather support the hypothesis of non-specific activation pattern in negative and positive emotions (Naumann *et al.*, 1992, 1993; Schneider *et al.*, 1995; Breiter *et al.*, 1996; Schupp *et al.*, 1997; Beauregard *et al.*, 1998; Phelps *et al.*, 1998). In addition it would be helpful to know the time-course of negative and positive emotional processing in orbitofrontal and prefrontal cortex. Even if negative and positive emotions are processed in similar neural structures they may differ in time-course (early or later orbitofrontal activation) and/or in functional connectivity (distinct functional connections between orbitofrontal cortex and other prefrontal cortical areas in negative and positive emotions).

According to Damasio (Damasio, 1994, 1995, 1997), emotions signify somatic and cognitive events before they are transformed into action. One may assume that distinct kinds of signification, either negative or positive, may be processed in different spatial and/or temporal ways from orbitofrontal to premotor/motor cortex. We therefore investigated spatial and temporal activation patterns in orbitofrontal, prefrontal and premotor/motor cortex during emotional-motor (positive and negative pictures associated with a motor response) and non-emotional-motor control (gray and neutral pictures associated with a motor response) conditions in healthy subjects combining functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG).

Techniques with high spatial (positron emission tomography or fMRI) and temporal (MEG) resolution have been advantageously combined before (Heinze *et al.*, 1994), particularly in activation with movements (Sanders *et al.*, 1996; Joliot *et al.*, 1998; Stippich *et al.*, 1998), but, to our knowledge, have never been combined in relation to emotional activation. Although there are several methodological problems in applying two techniques with different neurophysiological substrates,

hemodynamic (fMRI) and electromagnetic (MEG) activity, the above-cited studies have nevertheless yielded high coincidence between both kinds of signals and thus afford complementary information (Heinze *et al.*, 1994; Sanders *et al.*, 1996; Joliot *et al.*, 1998; Stippich *et al.*, 1998). Consequently combining spatial and temporal measures with fMRI and MEG during emotional activation may further reveal similarities and differences in physiological mechanisms in neural processing of negative and positive emotions.

## Materials and Methods

### Subjects

Healthy subjects (age  $25.9 \pm 6.1$  years, mean  $\pm$  SD; all right-handed) included 10 persons (5 women and 5 men). Subjects with a history of psychiatric, neurological or other serious physical illness; drug or alcohol abuse; or first-degree relatives with a history of major psychiatric or neurological disorders (as evaluated with the semistructured interview according to DSM IV) were excluded. No subject was taking regular medication.

Ethics approval and permission were obtained from the Ethics Committee of the University of Magdeburg. After complete and detailed description of the study to the subjects, written informed consent was obtained.

### Paradigm

#### Affective Stimulation

Affective stimulation was performed with pictures from the International Affective Picture System (IAPS) (Lang *et al.*, 1997) which was validated also on a German population (Hamm and Vaitl, 1993). Based on the large-sample valence (positive-negative) ratings, pictures were selected as negative (e.g. a mutilated face) or positive (e.g. smiling baby). Neutral (e.g. a book) pictures served as a control condition in order to control for potentially confounding features of the emotion-generating pictures such as emotionally irrelevant visual stimulation related to objects, scenes, etc., as well as attentional and arousal effects. In addition, gray pictures without any contours, patterns and content, showing only the colour gray homogeneously, served as a second control condition in order to control for arousal effects as elicited by visual contents, contours and patterns. Slide sets were matched for content/properties (colours, scenery, objects, people, close-ups of faces, animals), dominance (according to subjective ratings provided by IAPS) and arousal (according to subjective ratings provided by IAPS). Although such matching of contents/properties is not available by the IAPS itself, we nevertheless tried to match pictures as much as possible in orientation using the method of Irwin *et al.* (Irwin *et al.*, 1997). Even if the same content or scenery were not exactly available in another valence we nevertheless tried to match the respective picture with a picture containing a somehow related content, property or scenery. For example, a book was not matched with a picture that included people or animals, and vice versa. A picture with predominantly blue content was not matched with a rather red picture. Subsequently pictures differed only in emotional valence (positive, neutral, negative) but neither in dominance nor in arousal.

We employed 100 pictures from each condition (100 negative, 100 positive, 100 neutral, 100 gray) and presented them under computer control. Pictures were presented for 6 s respectively in blocks with 10 valence constant pictures (positive, negative, neutral and gray blocks); between the blocks there was a break of 3 s. The order of blocks was counterbalanced with regard to emotional valence in order to control for potential order effects. Subsequently 40 blocks, each consisting of 10 valence-constant pictures, were presented in a counterbalanced order so that positive, negative, neutral and gray blocks were alternating. Blocks were counterbalanced between subjects as well as across fMRI/MEG investigations. Each picture was presented for 6 s and appeared on a screen with a central fixation point (in both fMRI and MEG in order to avoid eye movements; see also below), and was switched automatically to the next picture. Subjects (all right-handed) had to press a touch switch by means of abduction of the right index finger as soon as a new picture appeared.

### Paradigm Implementation

For both MRI and MEG, the visual stimuli were projected automatically via a computer and a back-projection television system.

**MRI.** In MRI these projected stimuli were then focused via a biconvex lens so that subjects wearing a binocular could see the pictures inside the scanner. The heads of the subjects were restrained using a vacuum-compressed surgical pillow. Subjects were instructed not to move their eyes or other parts of their body. Optimal position of the binocular with fixation (in order to avoid eye movements) as well as of the head and the body were adjusted individually in order to avoid eye and head movements.

**MEG.** The subject was sitting in a wooden chair in a magnetically shielded room (Low Temperature Laboratory, University of Magdeburg), with the forearm pronated on the armrest. Pictures were presented on a normal screen located 1 m in front of the subject. The optimal position of the subject with regard to the screen was adjusted individually such that they were not forced to move their eyes either horizontally or vertically in order to watch the pictures. The subjects were requested to keep their eyes open and to fixate the middle of the screen in front of them. They were asked not to move either their eyes or other parts of the body before, during and after their finger movements.

### Instructions Given to Subjects

The experiment took place in four sessions. Session 1 acquainted fMRI and MEG subjects with the scanner and the experimental procedure. Sessions 2 and 3 were the actual scanning sessions. The order of investigations (first MEG then MRI or inverse) was counterbalanced for subjects within each group, controlling for potential order effects. In session 4, subjects made ratings of the pictures to which they were exposed.

Prior to all sessions, subjects were told that they will view various pictures with different emotional contents. Furthermore, subjects were informed they (all subjects) would receive an i.v. injection of saline before fMRI/MEG since the subjects of the current study were used as a placebo-control group as part of an ongoing study.

Subjects were further asked to remain as motionless as possible to minimize MEG and fMRI movement artifacts. They were told to avoid eye movements before, during and after their finger movements and to fixate a central fixation point on the screen in MEG and the binocular in fMRI. If they had the urge to move either their body or their eyes they were instructed to do this during the 3 s break between the blocks. All subjects understood they could terminate the experiment at any time without explanation. Before actual fMRI and MEG scanning (i.e. before session 2), subjects were given the opportunity to practise prior to the experiment with 20 test pictures.

### Behavioral and Psychological Monitoring

Reaction time –the time from the appearance of a new picture to the execution of the finger movement (i.e. press on the touch switch) – was registered. For analysis we calculated the means of reaction time for each condition (i.e. positive, negative, neutral, gray) and compared them statistically using Friedman tests for dependent samples. We choosed reaction time as a behavioral measure of emotional valence since it is known that the time necessary for movement preparation and initiation depends on the respective functional context (other movements, concomittant visual stimuli, etc.); the more complex the content (and the movement), the longer the reaction time (Kristeva *et al.*, 1991; Kristeva-Feige *et al.*, 1997; Naito *et al.*, 1998). Hence we expected differences in reaction times between negative, positive and neutral (i.e. more complex) pictures on the one hand, and gray (i.e. less complex) pictures on the other hand. Assuming different correlation patterns between both emotional conditions we in addition performed correlational analysis between subjective ratings of the pictures and reaction times for each condition (negative, positive, neutral, gray) using Spearman correlation analysis with Bonferroni correction (significance level of  $P = 0.0042$ ).

In order to control for pre-experimental psychological states, which might influence emotional induction, all subjects had to fill out the Bf-s, the Befindlichkeitsskala (Zerssen, 1976), a well-validated instrument for

self-evaluation of actual psychological state. Furthermore each subject was retrospectively asked whether the injection had any influence on their psychological state; all subjects denied that it had.

Pictures from the IAPS were subjectively rated for valence, dominance and arousal with the Self-Assessment Manikin (SAM) (Lang, 1980). IAPS ratings of were done after fMRI/MEG investigations. Subjective ratings of the different conditions were compared with those obtained by Hamm and Vaitl, who validated the IAPS for a German population (Hamm and Vaitl, 1993). Due to the influence of the magnetic field we were unfortunately unable to obtain vegetative measures of emotional responses (skin resistance, etc.) during scanning.

### Functional MRI

#### Data Acquisition

The images were acquired in a Bruker Biospec 3T/60cm head scanner equipped with a quadrupolar birdcage head coil. Before scanning, the nasion and the right and left preauricular points were marked with paramagnetic markers in order to project dipoles from MEG on anatomical and fMR images. The subjects heads were immobilized with a vacuum cushion with attached earmuffs. An imaging session started with low-noise [sound pressure level (SPL) 62 dBA], low-contrast FLASH images in mediosagittal directions. The use of a FLASH sequence offers the possibility to slow down the gradient switching. Together with an optimized excitation pulse and modified spoiler gradients the final 'low-noise' imaging sequence, focused on a few slices, produced a noise peak level of 58 dB SPL at the position of the ear.

Five contiguous axial planes of the whole frontal lobe including the medial and lateral frontal cortex, the motor and premotor cortex, the orbitofrontal cortex and the anterior cingulate (i.e. from orbitofrontal cortex and ventricles up to central sulcus) were chosen for functional imaging (i.e. thickness of 8 mm, 160 mm field of view, and  $64 \times 64$  matrix size) (see Fig. 1).

Two hundred and forty functional images for each slice were collected using a low-noise conventional gradient echo sequence (SPL 58 dBA,  $T_E$  40 ms,  $T_R$  313 ms, flip angle,  $8^\circ$ ) with medium high resolution ( $2.5 \times 2.5 \times 8$  mm) within 45 min. For each block of visual stimuli (i.e. 10 valence-constant pictures each presented for 6 s, resulting in a total duration of one block of 1 min; see above) six images (i.e. each including all five slices) were acquired (i.e. each image lasted 10 s), resulting in a total acquisition time of 1 min (i.e.  $6 \times 10$  s) per block. Consequently 60 images were acquired for each condition (i.e. 10 blocks of positive, negative, neutral and gray pictures respectively), resulting in a total of 240 images and an acquisition time of 45 min.

High  $T_1$ -contrast imaging (MDEFIT) was used to obtain anatomical landmarks with high three-dimensional resolution and immediately followed fMRI with the following parameters: field of view 256 mm, slice thickness 2.25 mm, 64 slices, in-plane matrix size  $256 \times 256$ . On the basis of these anatomical images, localization of slices/activity in fMRI and dipoles from MEG were determined.

#### Image and Statistical Analysis

Data were analyzed as follows. First, subject movement was monitored using the AIR package. Data were selected for further analysis on the basis of the absence of motion artifacts. In orientation on the standard (Bandettini *et al.*, 1993, Sanders *et al.*, 1996) subjects with head movements  $>2$  mm and or  $>1^\circ$  were excluded from initial analysis ( $n = 2$ ). Since both subjects showed only slightly increased movements (2.4 mm and  $1.2^\circ$ ; 2.0 mm and  $0.9^\circ$ ) we first ran an analysis without them and then included them into the analysis in order to increase the number of subjects; this did not result in any changes in the results. Moreover, we compared the subjects below the artifact rejection rate ( $n = 8$ ) with those above the artifact rejection rate ( $n = 2$ ) and could not find any differences. In agreement with previous methods used (Irwin *et al.*, 1997; Lang *et al.*, 1998) we finally checked all subjects ( $n = 10$ ) for presence/absence of eye movement artifacts in vertical and horizontal EOG as measured in MEG (see below). None of the subjects included into final analysis ( $n = 10$ ) showed any alterations in EOG as can be seen in Figure 3. Hence the results reported are the ones from the second analysis with 10 subjects, which included the two subjects initially excluded.

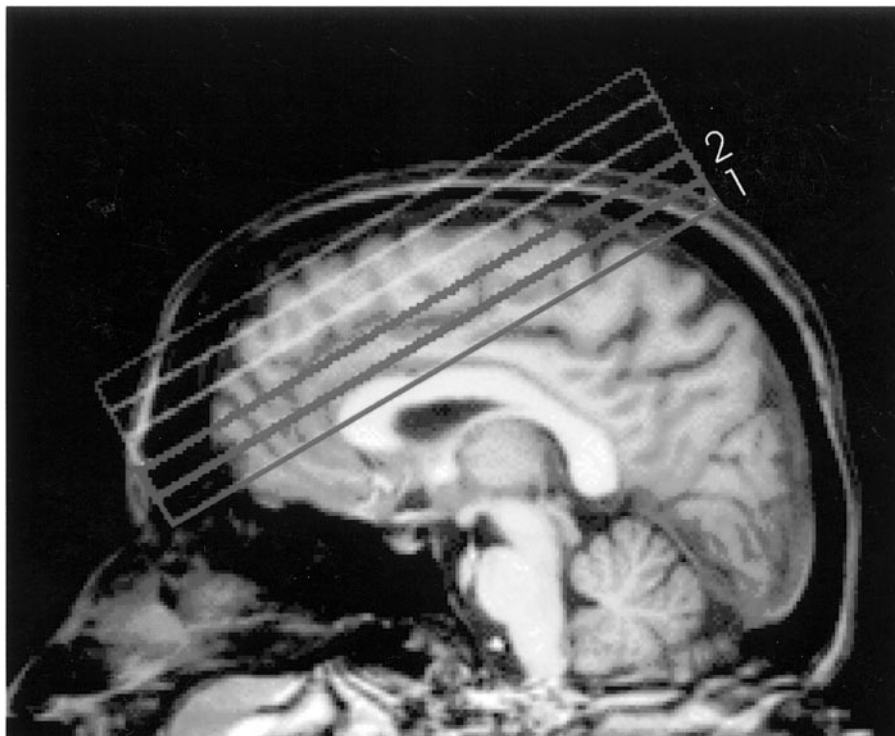
Second, activation analysis was performed by computing the correlation coefficients between voxel time response and box-car waveform representing the stimulation. Voxels that had correlation coefficients with a statistical significance  $P > 0.05$  were rejected. The functional images were then superimposed on the individual anatomical reference images (Gaschler-Markewski *et al.*, 1997). In each slice, different anatomical regions of interest (ROIs) were outlined individually on the respective anatomical MRI without functional overlays. For each individual, 11 brain regions (see Fig. 1) were defined individually by landmarks (i.e. the respective gyri) and identified according to the Talairach atlas (Talairach and Tournoux, 1988) as covering the orbitofrontal [Brodmann area (BA) 11, 12], lateral prefrontal (BA 9, 45, 46, 47), medial prefrontal (BA 8, 9, 10), premotor (BA 6) and motor (BA 4) cortex on the right and left side respectively, and anterior cingulate cortex (BA 24, 32) bilaterally (Kammer *et al.*, 1997). Since the orbitofrontal cortex is close to regions with a high potential for magnetic susceptibility artifacts we, in agreement with previous work (Breiter *et al.*, 1996, 1997), checked that orbitofrontal activations did not overlap regions of susceptibility artifact; if they did (i.e. if artifacts were as high or even higher than stimulus-correlated activity) they were excluded from analysis (see also Methodological limitations). Even if the determination of ROI according to the Talairach-Tournoux atlas has considerable shortcomings (especially with regard to the ventral prefrontal cortex), we nevertheless applied it since most current imaging studies use it for anatomical determination, and our localizations could thus be compared with the other studies. In addition, use of Talairach determination proved to be helpful in comparing localizations obtained in fMRI with those from MEG (see below).

Activity in these ROIs in both hemispheres was analyzed by correlation analysis (Bandettini *et al.*, 1993) to obtain a statistical parametric map. Such a map displays the spatial distribution of the Z-score for each of the differences or 'constrasts' positive-negative, positive-neutral, positive-gray, negative-neutral, negative-gray and neutral-gray. These maps were thresholded ( $P < 0.001$ ) ( $P < 0.05$  for the spatial extent of the activation foci) and overlaid onto our anatomical template image to attribute each activation focus to an anatomical area. To orientate standards with regard to thresholds, two kinds of analysis were performed: one without correction for multiple comparisons ( $P < 0.001$ ), and one with correction for multiple comparisons ( $P < 0.01$ ), in agreement with Lang *et al.* (Lang *et al.*, 1998) who used a similar procedure. Since both kinds of analysis revealed similar results, activated voxels seem to represent 'true' activations rather than artifacts of multiple comparison. Percentages of significantly activated voxels and intensity-weighted volumes (IWVs) (the product of the absolute number of voxels and the average signal change in each region in all slices) were determined for positively and negatively correlated activations (Gaschler-Markewski *et al.*, 1997). In addition to absolute numbers of positive and negative IWVs (see Table 1), we determined the relative activation (positive IWVs)/deactivation (negative IWVs) strength of prefrontal cortical regions with highest, intermediate and lowest activity within the respective contrast (see Table 2). The right and left side of each region were added and divided by two and compared to the other regions so that finally distribution of activity across the various prefrontal cortical regions within that particular contrast was obtained; comparisons of relative activation strength across the various contrasts remain impossible. For interpretation of results for each contrast separately one should thus put both kinds of presentations – absolute number of positive/negative IWVs in each prefrontal region (Table 1) and relative activation strength across prefrontal regions (Table 2) – together. Correlation analyses using Spearman rank correlation tests were performed to calculate relations between fMRI signal (IWV) in the various ROIs and reaction times (Naito *et al.*, 1998).

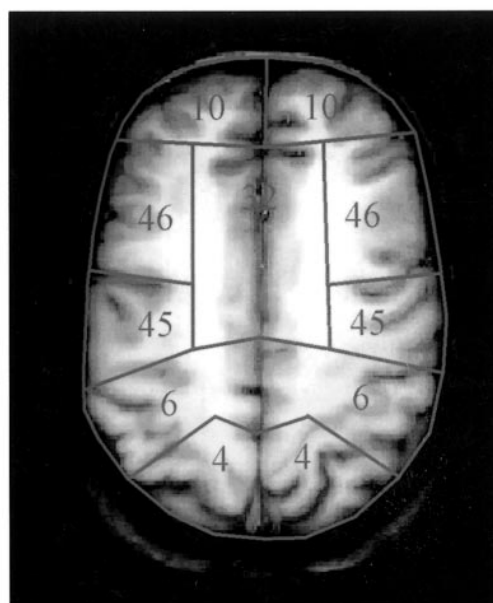
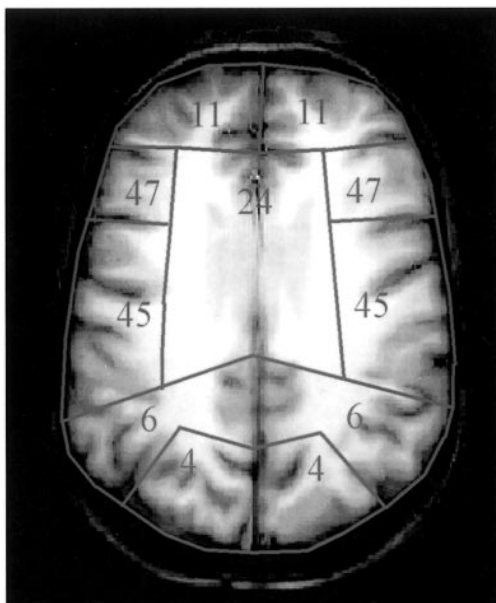
#### Analysis of Structural Connectivity in Primate Prefrontal Cortex

In order to corroborate on anatomical grounds the emerging results (see below) of a dissociation of primate prefrontal cortex into medial and lateral groups, we statistically investigated the connectivity patterns of the prefrontal areas. In analogy to Young *et al.*'s analysis of the 'visual streams' (Young *et al.*, 1995), we characterized the dichotomization of prefrontal cortical areas into two groups by a two-sided criterion: (i) areas should be significantly more connected within the groups than between the groups, and (ii) areas should be significantly more disconnected between the groups than within the groups.





A



B

**Figure 1.** Placement of slices and determination of regions of interest (ROIs). (A) Midsagittal view of slice placement ( $T_1$ -weighted spin-echo sequences). Five images of contiguous oblique-axial planes with slice thickness of 8 mm and  $64 \times 64$  voxels in plane were obtained from the whole frontal lobe. Slice locations were  $\sim 40^\circ$  relative to the AC-PC line. (B) In each slice, different anatomical ROIs were outlined anatomically without functional overlays. Regions were defined by landmarks according to Talairach coordinates (Talairach and Tournoux, 1988) covering the orbitofrontal, lateral prefrontal, medial prefrontal, cingular, premotor and motor areas. Numbers within the different regions show the respective Brodman area. The two lowest slices, as indicated by (1) and (2) in (A), are shown with their respective ROIs.

This standard criterion for anatomical dissociation of two areal groups can easily be evaluated by performing a chi-squared test on the respective connectivity data. As data on human cortical connectivity are not available, we addressed this issue generally for primate prefrontal cortex by using macaque connectivity data from the database CoCoMac (<http://www.hirn.uni-duesseldorf.de/~rk/Cx/CoCoMac.htm>). This rela-

tional database currently contains almost 5000 experimental findings on corticocortical connectivity collated in a standardized manner from published tracing studies. Using objective relational transformation (ORT), CoCoMac is able to convert data between different parcellation schemes independent of spatial coordinates (Stephan and Kötter, 1999; Stephan *et al.*, 1999). In order to control for potential influences of the

resolution of the chosen parcellation scheme on the result of our statistical test, we used CoCoMac to transform the data into two different maps, the traditional (and rather coarse) map of Walker (Walker, 1940), and the scheme of Carmichael and Price (Carmichael and Price, 1994), which is considerably more fine-grained for orbital and medial parts of prefrontal cortex. For both maps, we assigned each area either to a lateral or a medial group. An area was assigned to the lateral group if it was entirely situated on or encroached substantially onto the lateral convexity, i.e. for Walker's map the lateral group comprised areas 8A, 8B, 9, 12, 45, 46, whereas for the scheme of Carmichael and Price it contained areas 12r, 12l, 10o, 45, 46, 8 and 9. All other prefrontal areas were assigned to the medial group.

## Magnetoencephalography (MEG)

### Experimental Procedure

A 148-channel (i.e. arranged in a helmet-like configuration) DC-SQUID neuromagnetometer (Magnes 2500 WH, Biomagnetic Technologies, San Diego, CA), covering the whole scalp, recorded the brain's magnetic fields. This device employs 74 pairs of two orthogonal figure-of-eight planar first-order gradiometers, measuring at each location the two orthogonal derivatives, one along the latitudes and the other along the longitudes, of the radial magnetic field component  $B_z$ . With this configuration, the largest signal can be detected just above the source current. The electro-oculogram (EOG) was recorded using Ag/AgCl electrodes. To monitor eye movements and the possible spread of brain activity below the orbit, one measurement between the right/left infraorbital and the right/left mastoid was adopted in addition to the conventional vertical and horizontal electro-oculograms from both eyes. Surface EMG associated with abduction of the index finger was recorded from two electrodes placed ~2 cm apart over the right first dorsal interosseus muscle.

A subset of MEG channels, EOG and EMG were displayed on a screen continuously, so that the task performance and the vigilance of the subject could be monitored.

A three-dimensional Cartesian head coordinate system was defined for each subject based on three anatomical landmarks: left and right preauricular points as well as nasion. In this three-dimensional head coordinate system the positive  $x$ -axis passed through the nasion (anterior-posterior direction) and the positive  $y$ -axis through the left preauricular point (medial-lateral direction), whereas the  $z$ -axis (representing the inferior-superior direction) was perpendicular to the point of bisection between the  $x$ - and  $y$ -axes. Position and orientation of the sensor as well as the head shape with respect to this coordinate system were measured with a three-dimensional digitizer before and after each recording session.

**Signal Analysis.** The recording passband was 0–50 Hz for MEG, 0.01–100 Hz for EOG (6 dB points) and 30–3000 Hz for EMG. The signals were digitized at 254.31 Hz and afterwards segmented into stimulus-locked epochs of 2.0 s duration (1800 ms pretrigger interval). Off-line reduction of environmental noise was performed through subtraction of the weighted signals from three reference channels. Automatic rejection level of field amplitudes  $>3$  pT/cm was used to exclude magnetic artifacts; for EOG the rejection level was 100  $\mu$ V. Spontaneous activity was continuously stored on a magneto-optical disk for later off-line analysis. The averaged epochs were finally filtered with a 45 Hz low pass in combination with a 50 Hz Notch filter.

**Off-line Analysis.** The spontaneous signals were analyzed off-line to obtain precise alignment with the EMG onset. Signals associated with each EMG burst were reviewed visually, and the epochs containing eye motion artifacts, ambiguous EMG bursts or other artifacts were omitted from the analysis. Only those trials without any eye motion artifacts containing movements with the same abrupt onset rise time and the same shape as seen in the rectified EMG were utilized for further analysis. A total of at least 70 artifact-free trials were averaged for each experimental condition (positive, negative, neutral, gray), otherwise ( $<70$  artifact-free trials per condition) the subject was excluded from the study (see above: Exclusion criteria). There were neither significant differences nor any trends in number of eye artifacts between the four conditions (negative,

positive, neutral, gray); hence emotional conditions did not induce more eye artifacts than non-emotional conditions. Subjects whose head positions differed by  $>1$  cm between the beginning and the end of the session, as measured with the three head positions (nasion, preauricular left and right; see above) were excluded ( $n = 1$ ). After digital low-pass filtering at 45 Hz and a 50 Hz Notch filter, the signals were subjected to amplitude measurements within epochs of 50 ms within a time window of analysis of 2200 ms ( $-2000$  to  $+200$  ms), of which the first 200 ms were used for determining the baseline. The processed data were also utilized for construction of isocontour maps, and, finally, for source identification. Occipital channels were excluded for analysis of amplitudes and source identification in order to avoid interference between visual processing in occipital regions and early emotional processing in frontal areas.

**Isocontour Maps and Source Identification.** Isocontour maps of the field amplitude were constructed from the measured data at selected latencies (200 ms epochs within the time window of analysis) using linear interpolation.

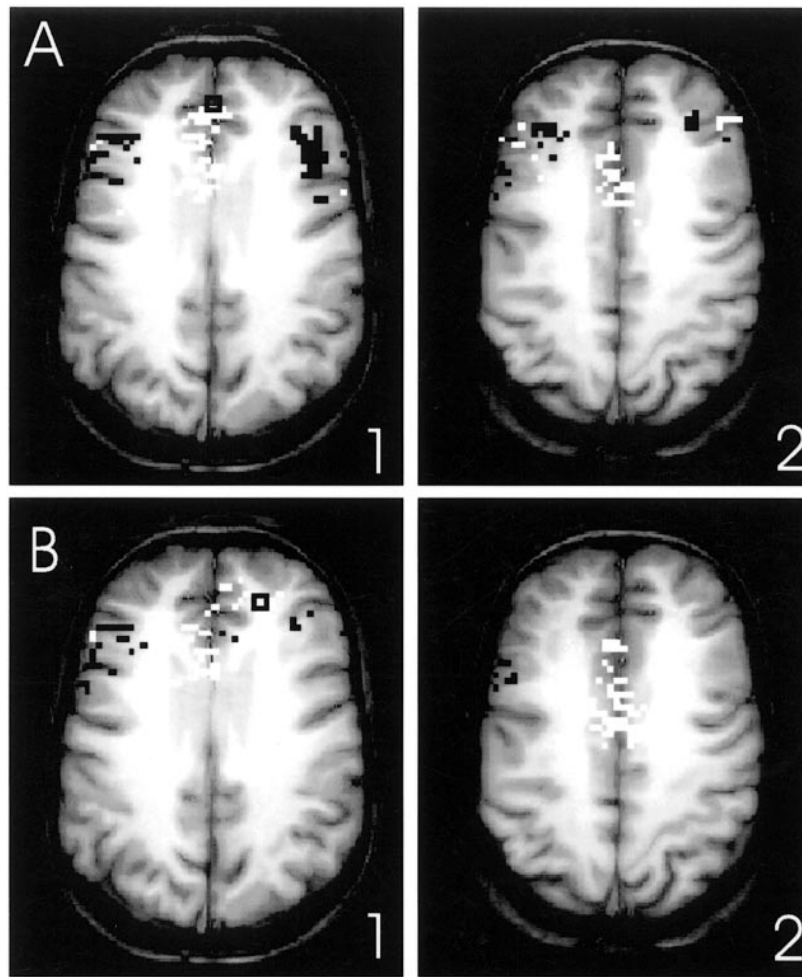
To identify sources underlying the measured signals, the signal distributions were modeled using the model of a moving dipole (MD) embedded in a homogenous spherical volume conductor. The centre of the volume conductor was evaluated by approximating the surface of the scalp underneath the gradiometer system by the above-mentioned sphere. The model (strength, position, orientation) parameters were optimized by means of an iterative least-squares procedure. The MD analysis was performed for each 50 ms epoch within the time window of analysis. Only MDs accounting for  $>60\%$  of the field variance and with a goodness-of-fit value  $>85\text{--}90\%$  were accepted. For each 50 ms epoch within the window of time analysis, the MD with the best goodness-of-fit value was taken as the representative one.

**MRI-MEG Integration.** (i) Dipole locations were projected onto the corresponding three-dimensional anatomical MRI scan (see above for further details of anatomical MRI scan). To identify the nasion and the two preauricular points in the MRI, paramagnetic markers (Nitro capsules) centered on these points were fixed on the scalp. The markers were easily identified in the MR images and served as reference points for localizing the estimated dipole locations in the MRI data sets. Prefrontal, premotor and motor cortical areas were identified in anatomical MRI as described in the Talairach-Tournoux atlas (Talairach and Tournoux, 1993). (ii) Functional MR images were matched and projected on the respective individual three-dimensional anatomical MRI scan with the respective dipole locations in order to compare anatomical localizations between dipoles and fMRI signals. (iii) The ROI in fMRI, within which the dipole could be localized, and its nearest local maximum of activation in the slice indicated by MEG, were determined in agreement with the method applied by Sanders *et al.* (Sanders *et al.*, 1996), which compared to other methods of comparison between MEG and fMRI signals proved to be the most valid one. However, interpretation remains limited since, firstly, both kinds of signals must be physiologically distinguished; and secondly, comparison reflects only anatomical closeness or distance, and any physiological interpretation should be avoided. Hence, interpretation is limited and rather relative. (iv) Talairach coordinates of both estimated dipoles and corresponding regional activation clusters in fMRI were determined in reference to three-dimensional anatomical MRI. (v) Talairach coordinates for dipoles and corresponding fMRI signals were compared with each other to measure differences in anatomical localization in millimeters (see Table 4). Although these values seem to be a quite exact interpretation, due to the above-mentioned reasons, the results do, however, remain limited and rather relative, as they only reflect anatomical closeness or distance within one or several regions between both kinds of signals.

## Results

### Behavioral Measures

Mean reaction times were lowest during gray pictures ( $443.10 \pm 139.23$  ms) and higher during negative ( $520.95 \pm 160.40$  ms), positive ( $520.01 \pm 178.31$  ms) and neutral ( $529.29 \pm 184.36$  ms)



**Figure 2.** Localization of fMRI activity and the dipole of the early magnetic field (EMF) from MEG each matched to the same individual anatomical MRI image. (A) Activated areas and dipole of early magnetic field (–1685ms) in negative emotions. (B) Activated areas and dipole of early magnetic field (–1447ms) in positive emotions. (1) Lowest slice (see also Fig. 1). (2) Second lowest slice (see also Fig. 1). White pixels = positive correlated voxels; black pixels = negative correlated voxels; squares = dipole of the early magnetic field (EMF). The fMRI activity and the early magnetic field dipoles are localized in adjacent brain areas. EMF dipoles and nearest local maximum of regional activation in fMRI are separated by 7.2 mm in negative emotions (A) and by 9.1 mm in positive emotions (B). Note the strong medial orbitofrontal activity in negative emotions, whereas in positive emotions almost no orbitofrontal activity can be observed; this is further underlined by localization of the dipoles of the early magnetic field in corresponding regions respectively.

conditions. Variance analysis, however, did not show any significant difference ( $P = 0.731$ ) between the four conditions.

Pre-experimental psychological states as measured with the Befindlichkeitsskala (BFs) (see Materials and Methods) revealed a value of  $13.42 \pm 5.05$ , indicating no major stress in current psychological state. Ratings of valence, dominance and arousal of pictures from IAPS (see Materials and Methods) in healthy subjects did not differ from ratings in the already investigated healthy population (Hamm and Vaitl, 1993; Lang *et al.*, 1997). The heart rate as a physiological measure, which could be obtained in MEG only, showed no significant differences between the four conditions ( $73.3 \pm 4.5$  min in negative emotions;  $69.5 \pm 3.6$  in positive emotions;  $68.8 \pm 3.8$  min in neutral pictures;  $62.3 \pm 3.6$  min in gray pictures).

### Cortical Activation in fMRI

Activation signals in fMRI showed clusters of activation in orbitofrontal, lateral prefrontal and premotor cortical areas, corresponding to BA 11 and 12 (orbitofrontal), BA 9, 45, 46 and 47 (lateral prefrontal), and BA 6 (premotor), whereas the other prefrontal/frontal areas such as cingulate cortex (BA 24, 32), medial prefrontal cortex (BA 8, 9,10) and motor cortex (BA 4)

were less activated (see Table 1 and Fig. 2). In general, activation was much stronger in contrasts involving positive or/and negative emotional pictures than in non-emotional contrasts (gray–neutral) (see Table 1). We did not observe differences in lateralization between the four experimental conditions (gray, neutral, positive, negative) (see Fig. 3) or different activation patterns in women and men.

Contrasts involving negative emotional pictures (negative–gray, negative–neutral, negative–positive) showed strong activation clusters, particularly in medial orbitofrontal cortex (BA 11, 12), and less strong clusters in lower lateral prefrontal cortex (BA 9, 45, 46, 47) (see Tables 1 and 2 and Fig. 2). In addition to positively correlated cortical activity, a high proportion of negatively correlated activity was particularly visible in contrasts involving negative emotional pictures, whereas less activity was observed in the other three conditions (positive, neutral, gray) (see Fig. 2 and Tables 1 and 2). Negatively correlated IWVs in contrasts involving negative emotional pictures (negative–gray, negative–neutral, negative–positive) were strongest in upper lateral prefrontal cortex (BA 9, 45, 46, 47) cingulum (BA 32) and premotor cortex (BA 6) (see Tables 1 and 2).

Contrasts involving positive emotional pictures (positive–



**Table 1**

Positively and negatively correlated intensity-weighted volumes in positive and negative emotional contrasts

ROI		Emotional contrast											
		Positively correlated IWW						Negatively correlated IWW					
		N-G	P-G	Ng-G	Ng-N	P-N	Ng-P	N-G	P-G	Ng-G	Ng-N	P-N	Ng-P
Orbitofrontal cortex (BA 11, 12)	right	84 (10)	128 (9)	280 (13)	188 (12)	66 (8)	125 (10)	-66 (10)	-229 (15)	-246 (10)	-111 (9)	-156 (9)	-90 (6)
	left	72 (9)	109 (10)	238 (10)	176 (10)	65 (8)	139 (11)	-48 (4)	-156 (10)	-318 (13)	-176 (8)	-133 (8)	-103 (5)
Lateral prefrontal cortex (BA9, 45, 46, 47)	right	135 (17)	505 (38)	317 (29)	148 (13)	319 (25)	122 (9)	-	-268 (20)	-680 (29)	-206 (10)	-	-100 (9)
	left	196 (22)	682 (40)	339 (25)	159 (19)	529 (30)	132 (10)	160 (10)	-230 (10)	-772 (31)	-358 (12)	113 (10)	-134 (10)
Anterior cingulate cortex (BA 24, 32)		40 (9)	95 (10)	136 (11)	48 (6)	78 (10)	80 (9)	-30 (6)	-46 (4)	-248 (20)	-178 (10)	-64 (7)	-60 (6)
Medial prefrontal cortex (BA 8, 9, 10)	right	86 (10)	160 (20)	140 (15)	52 (6)	119 (14)	110 (10)	-44 (6)	-96 (9)	-164 (10)	-90 (8)	-60 (8)	-87 (5)
	left	94 (11)	166 (18)	190 (18)	58 (7)	105 (10)	119 (13)	-30 (4)	-86 (6)	-184 (11)	-136 (10)	-70 (9)	-70 (9)
Motor cortex (BA 4)	right	51 (8)	337 (29)	105 (10)	66 (8)	105 (10)	79 (6)	-29 (5)	-94 (10)	-290 (20)	-68 (6)	-46 (5)	-45 (6)
	left	105 (10)	440 (30)	148 (9)	58 (8)	108 (11)	82 (9)	-68 (9)	-83 (8)	-326 (18)	-60 (6)	-54 (4)	-50 (5)
Premotor cortex cortex (BA 6)	right	14 (3)	120 (14)	30 (6)	28 (4)	259 (19)	50 (6)	-40 (6)	-48 (7)	-136 (10)	-39 (4)	-36 (4)	-95 (8)
	left	17 (4)	122 (15)	46 (7)	30 (5)	330 (25)	61 (7)	-80 (8)	-59 (6)	-156 (12)	-48 (5)	-40 (4)	-105 (7)

IWW, intensity weighted volume (product of percentage of activation signal and volume in  $\mu\text{l}$ ); N, neutral; G, gray; P, positive; Ng, negative; BA, Brodmann area. Voxel size = 50  $\mu\text{l}$ . Standard deviations in parentheses.

**Table 2**

Intersubject comparison of relative activation strength in prefrontal cortical regions in negative and positive emotions

	Orbitofrontal cortex (BA 11, 12)	Lateral prefrontal cortex (BA9, 45, 46, 47)	Anterior cingulate cortex (BA 24, 32)	Medial prefrontal cortex (BA 8, 9, 10)	Motor cortex (BA 4)	Premotor cortex cortex (BA 6)
Negative emotions (negative-neutral)	+++++/-	+/-	+++/-	+++++/-	+++/-	+/-
Positive emotions (positive-neutral)	+/-	+/-	+++/-	+++++/-	+++++/-	+++/-
Negative-positive	+++++/-	+++/-	+++/-	+++++/-	+/-	+++/-

+, positively correlated IWNs; -, negatively correlated IWNs; + to +++++, relative number of positive IWNs among prefrontal regions; - to -----, relative number of negative IWNs among prefrontal regions; BA, Brodmann area.

gray, positive-neutral, positive-negative) showed strong activation clusters, particularly in lower lateral prefrontal cortex (BA 46, 47), and less strong clusters in medial orbitofrontal cortex (BA 11, 12). In addition, positive emotional stimulation led to quite strong activation in premotor cortex which was not found in negative emotions (see Tables 1 and 2 as well as Fig. 2). Negatively correlated activity in contrasts involving positive pictures (positive-gray, positive-neutral) was strongest in orbitofrontal cortex (BA 11, 12) and less marked in lateral prefrontal cortex (BA 9, 46) (see Tables 1 and 2 as well as Fig. 2).

The negative-positive contrast showed the strongest positively and negatively correlated IWNs in orbitofrontal and lateral prefrontal cortex as well as in premotor cortex (only negatively correlated IWNs) (see Tables 1 and 2), further underlining the importance of these cortical regions in neural processing of positive and negative emotions.

In summary, negative and positive emotional pictures led to different activation patterns in orbitofrontal, lateral prefrontal and premotor cortex. Negative emotional pictures induced strong activation (i.e. positively correlated IWNs) in medial orbitofrontal cortex and marked negatively correlated activity in lateral prefrontal cortex, whereas positive emotional stimulation showed an inverse pattern with strong activation in lateral prefrontal cortex and marked negatively correlated activity in orbitofrontal cortex (see Table 2).

### Structural Connectivity in Primate Prefrontal Cortex

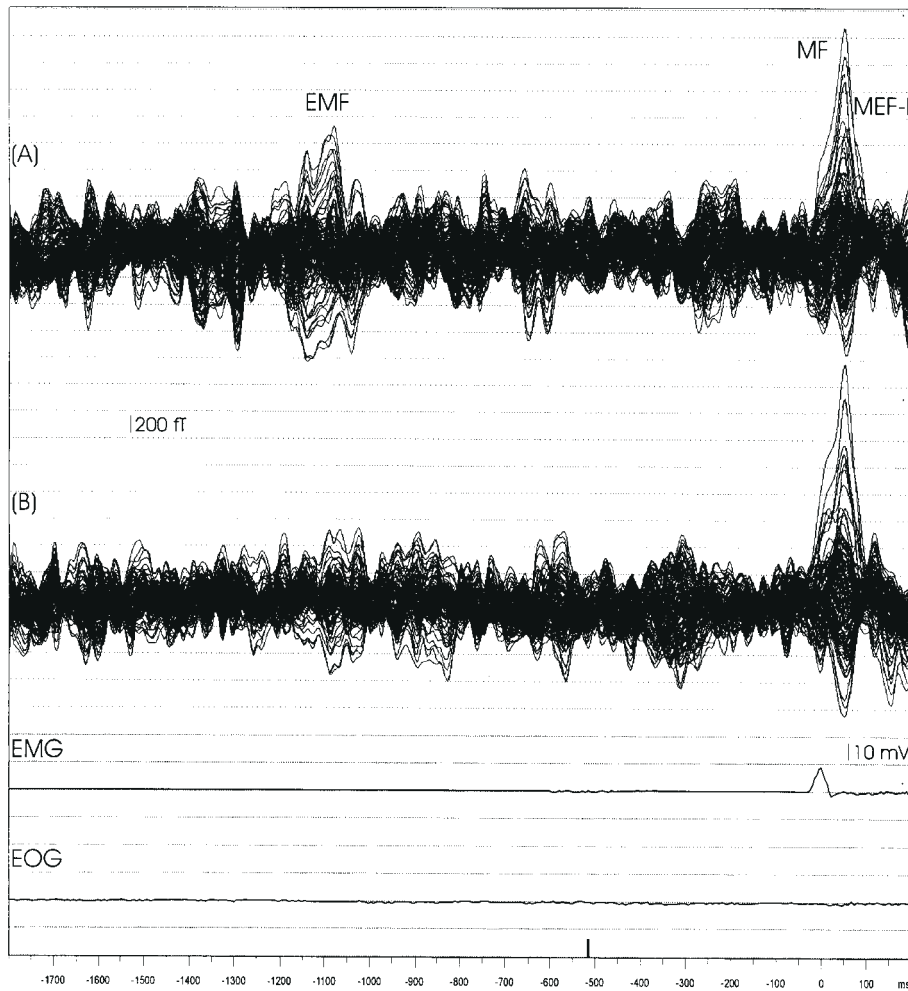
The CoCoMac database delivered 474 published reports on connectivity between the prefrontal areas of the map of Carmichael and Price (Carmichael and Price, 1994) (351 existing connections, 123 connections explicitly stated to be absent) and 104 reports for the respective areas of Walker's map

(Walker, 1940) (74 existing connections, 30 connections absent). Performing a chi-squared-test for each dataset according to the criterion of Young *et al.* (Young *et al.*, 1995) (see Materials and Methods), the null hypothesis was significantly rejected in both cases ( $P < 0.01$ ). Therefore, the anatomical connectivity corroborates the view that the primate prefrontal cortex is effectively dissociated into distinct lateral and medial groups of areas.

### Electromagnetic Signals in MEG

A representative magnetoencephalographic curve during index finger movement with emotional stimulation can be seen in Figure 3. All subjects typically showed a readiness field (RF), starting 500 ms prior to the movement, and a motor field (MF) (-50 to 50 ms) before and during movement execution. Both RF and MF were seen mainly over the left somatomotor area, followed by the movement-evoked fields MEFI (80-150 ms) and MEFII (150-200 ms), peaking at 100 and 180-200 ms respectively. The complete MEFII as well as MEFIII and PMF (postmovement field) could not be recorded because recording time was limited to 200 ms after movement onset (see Materials and Methods). The largest signal was reproducible over the left somatomotor area. This pattern of movement-related magnetic fields was observed in all subjects and showed no major differences between conditions (gray, neutral, positive, negative) (see Tables 3 and 4).

In addition to movement-related magnetic fields we observed early magnetic field alterations between -1700 and -1100 ms (early magnetic field; EMF) prior to the onset of movements (see Fig. 3) which were present only in positive and negative conditions but neither in gray nor in neutral pictures. This early magnetic field started earlier (-1700 ms) and was stronger in



**Figure 3.** Early magnetic fields and movement-related magnetic fields in negative and neutral emotions. (A) Magnetic fields in negative emotions. (B) Magnetic fields in neutral emotions. EMF, early magnetic field; MF, motor field; MEF-I, first motor-evoked field; EOG, electrooculogram; EMG, electromyogram. Magnetic fields are recorded from all 148 channels distributed over the whole scalp. Note the early onset and strength of early magnetic fields (EMF) in negative emotions and their absence in neutral emotions, whereas movement-related magnetic fields (MF, MEF-I) are present and almost similar in both conditions.

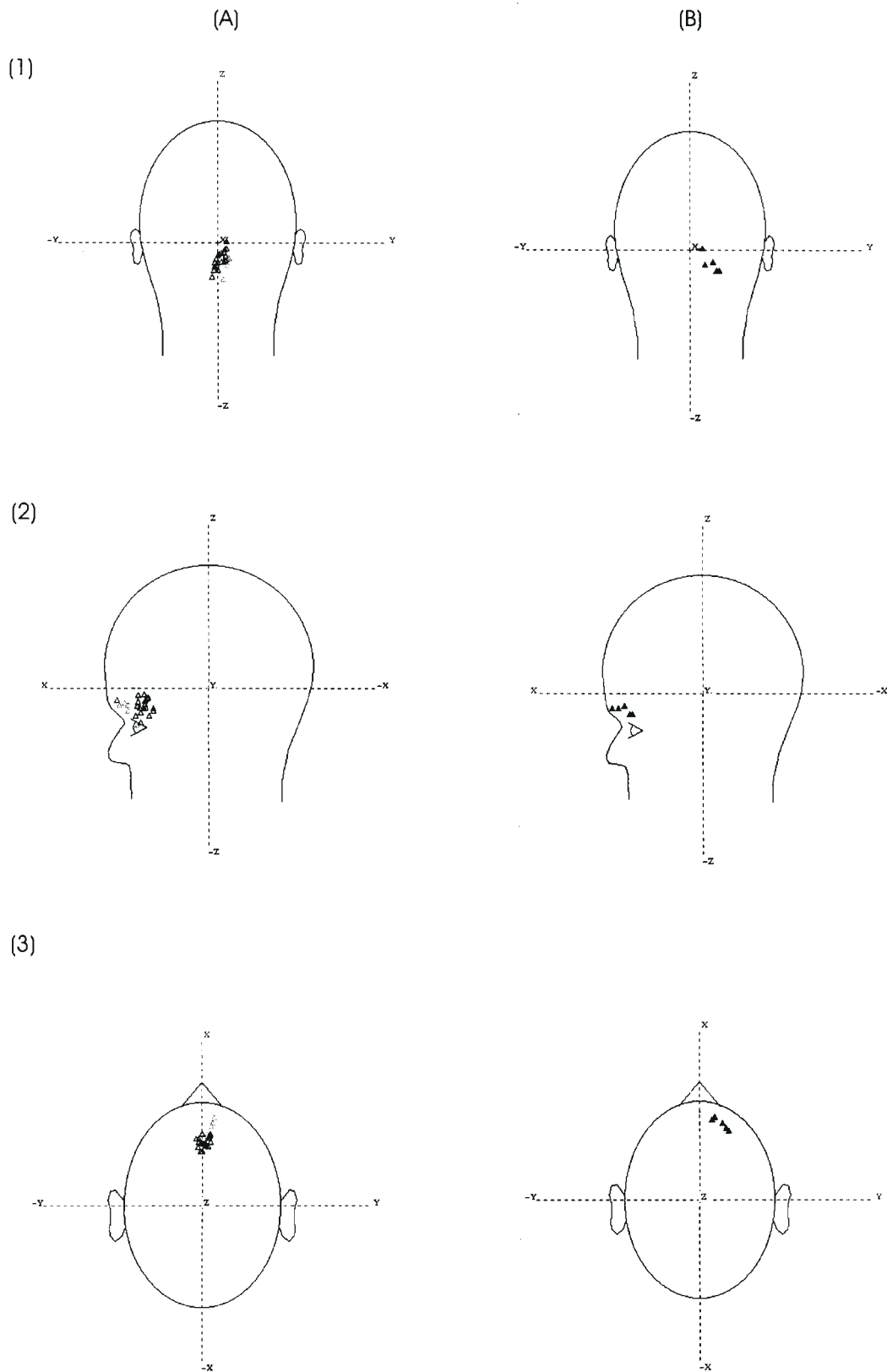
<b>Table 3</b> Intersubject analysis of strength and goodness of fit of magnetic fields and the corresponding dipoles						
Magnetic field	Condition	Time (ms)	RMS (fT) (mean ± SD)	Dipole RMS (fT) (mean ± SD)	Q (nAM) (mean ± SD)	GOF (>0.85) (mean ± SD)
Early magnetic field (EMF)	negative	-1709	35.95 ± 6.8	47.74 ± 14.6	45.84 ± 17.5	0.93 ± 0.06
		-1147	36.00 ± 9.8	49.01 ± 20.7	54.30 ± 19.0	0.89 ± 0.05
	positive	-1706	24.95 ± 5.0	37.32 ± 14.8	23.98 ± 14.7	0.86 ± 0.05
		-1135	33.23 ± 7.0	46.35 ± 12.7	39.73 ± 15.9	0.89 ± 0.04
Motor field(MF)	negative	-18	60.35 ± 7.5	74.32 ± 14.3	60.19 ± 20.9	0.92 ± 0.02
	positive	-17	65.84 ± 9.6	80.38 ± 17.4	58.20 ± 28.4	0.88 ± 0.04
	neutral	-18	60.48 ± 11.4	87.45 ± 12.7	62.45 ± 18.5	0.90 ± 0.03
	gray	-16	61.93 ± 7.9	81.54 ± 10.1	65.48 ± 15.9	0.90 ± 0.02
Motor evoked field I (MEF I)	negative	85	44.02 ± 8.7	56.92 ± 18.7	43.17 ± 25.6	0.86 ± 0.03
	positive	105	47.77 ± 8.4	55.11 ± 15.7	39.80 ± 13.5	0.85 ± 0.05
	neutral	97	45.30 ± 12.5	42.54 ± 8.7	26.17 ± 16.1	0.87 ± 0.04
	gray	89	50.02 ± 7.1	57.89 ± 7.0	33.44 ± 17.9	0.85 ± 0.05

RMS, root mean square; fT, femto Tesla; GOF, goodness of fit.

negative emotions than in positive emotions where it showed a later onset (-1500 ms) and a weaker strength (see Table 3 and Figs 2 and 4). In addition, exact anatomical localization of EMF

differed between negative and positive emotions. In negative emotions the largest EMF signal was reproducible in all subjects, except in one, over medial and anterior orbitofrontal cortical





**Figure 4.** Location of the fittest dipoles for the early magnetic field in a head coordinate system in negative and positive emotions. (A) Dipoles in negative emotions. (B) Dipoles in positive emotions. (1) Head viewed from behind ( $z$ - $y$  projection). (2) Head viewed from the right ( $x$ - $z$  projection). (3) Head viewed from above ( $x$ - $y$  projection). Triangles indicate the dipoles of early magnetic field (negative:  $-1700$  to  $-1100$  ms; positive:  $-1500$  to  $-1100$  ms). Neuromagnetic fields were recorded from the whole scalp using a 148-channel BTI system. The locations are shown as projections in a head coordinate system. Scale is 2 cm. The fittest dipoles in early magnetic fields were selected for each 50 ms epoch within the time windows given above.

**Table 4**

Intersubject comparison of anatomical localization of estimated dipoles in MEG and nearest local maximum of regional activation in fMRI in negative, positive and neutral conditions

Magnetic field	Condition	Anatomical location of nearest local maximum in fMRI (Brodmann area = BA)	MEG Talairach coordinates (mm, mean $\pm$ SD)			Global three-dimensional distances (mm, mean $\pm$ SD) between MEG and fMRI localization
			x	y	z	
Early magnetic field(-1700 to -1100 ms)	negative (-neutral)	medial orbitofrontal cortex (BA 11)	1.4 $\pm$ 0.2	44 $\pm$ 3	-21 $\pm$ 2	8.8 $\pm$ 2.4
	positive (-neutral)	mediolateral orbitofrontal cortex (BA 11, 47)	26 $\pm$ 4	36 $\pm$ 2	-22 $\pm$ 5	9.6 $\pm$ 4.3
	neutral (-grey)					
Motor field(-50 to +50 ms)	negative	left anterior motor cortex (BA 4)	-26 $\pm$ 3	-18 $\pm$ 4	54 $\pm$ 2	-
	positive	left anterior motor cortex (BA 4)	-25 $\pm$ 2	-17 $\pm$ 2	53 $\pm$ 3	-
	neutral	left anterior motor cortex (BA 4)	-26 $\pm$ 2	-18 $\pm$ 3	54 $\pm$ 4	-
Motor-evoked field I (80-150 ms)	negative	left posterior motor cortex (BA 4)	-34 $\pm$ 4	-24 $\pm$ 3	57 $\pm$ 2	-
	positive	left posterior motor cortex (BA 4)	-33 $\pm$ 1	-25 $\pm$ 2	58 $\pm$ 3	-
	neutral	left posterior motor cortex (BA 4)	-34 $\pm$ 2	-24 $\pm$ 4	57 $\pm$ 3	-

areas (BA 11), whereas in positive emotions it was rather located in more lateral parts of orbitofrontal (BA 11) cortex ( $n = 4$ ) or even in lower parts of lateral prefrontal (BA 47) cortex ( $n = 5$ ) (see Tables 3 and 4 as well as Figs 2 and 4).

A single-moving-dipole model (equivalent current dipoles; ECD) resulted in quite high goodness of fits (85–95%) and low residual variances for all magnetic fields components (EMF, RF, MF, MEFI), and hence we did not attempt to introduce additional ECDs. After anatomical overlay, ECDs reflecting RF, MF and MEFI could be located in anterior and posterior parts of motor cortex (see Table 4). ECDs reflecting the EMFs between -1700 and -1100 ms could be anatomically localized in medial and anterior orbitofrontal cortex (BA 11) in negative emotions ( $n = 9$ ), whereas in positive emotions they could be localized either in lateral orbitofrontal cortex (BA 11;  $n = 5$ ) or lower lateral prefrontal cortex (BA 47,  $n = 4$ ) (see Table 4 and Figs 2 and 4). Projections of ECDs on functional MR images in corresponding contrasts showed localization of early (-1700 to -1100 ms) dipoles, reflecting EMFs within clusters of activation in medial orbitofrontal (negative emotions), lateral orbitofrontal and lateral prefrontal (positive emotions) cortical areas (see Table 4 and Figs 2 and 4). Late (-500 to 200 ms) dipoles could be localized in premotor (supplementary motor area; BA 6) and motor (BA 4) cortex (see Table 4 and Fig. 4). However, fMRI activation signals in these areas were rather weak, probably due to the fact that the movement was the same in all four conditions so that consecutively there were no differences in cortical motor activation within the various contrasts. Distances between nearest local maximum activity in fMRI and early magnetic field dipole location were calculated and showed adjacent anatomical locations (see Table 4 and Fig. 2).

In summary, MEG signal analysis revealed the typical pattern of movement-related magnetic fields with a readiness field (RF), starting about -500 ms prior to movement onset, and motor fields (MF, MEFI) during and after movement onset. Dipoles of movement-related magnetic fields could be anatomically localized in anterior and posterior parts of primary motor cortex. In addition to movement-related magnetic fields, an EMF in early time windows (-1700 to -1100 ms) was observed only in positive and negative emotions but not in either of the control conditions (neutral, gray). Onset, strength and anatomical location of EMF differed between negative and positive emotions. EMF showed an earlier onset, a higher strength and a more medially oriented orbitofrontal location in negative emotions

than in positive emotions. Single ECDs for EMF were anatomically localized either in medial orbitofrontal cortex (negative emotions) or in lateral orbitofrontal/lower lateral prefrontal cortex (positive emotions), corresponding quite well to activation signals in the respective cortical area in fMRI.

#### Correlations between MRI/MEG Signals and Behavioral Measures

We correlated reaction times with subjective ratings and regional activation signals in fMRI/MEG using the Spearman rank correlation test with Bonferroni correction (significance level of  $P = 0.0042$  which is here equated with  $P = 0.05$ ). We obtained significant correlations between reaction times and subjective ratings only in negative emotions ( $r = 0.771$ ;  $P = 0.033$ ) but neither in positive emotions nor in the other two conditions (neutral, gray).

Concerning fMRI, regional activation signals were correlated with differences in reaction times between corresponding conditions. In the gray-neutral contrast marginally significant correlations were found between reaction time and right lateral prefrontal ( $r = -0.711$ ;  $P = 0.079$ ), right medial prefrontal ( $r = -0.676$ ;  $P = 0.095$ ), and left premotor ( $r = -0.713$ ;  $P = 0.070$ ) cortical activity. In addition, significant correlations were found only in negative emotions but not in contrasts involving positive emotions. Both contrasts, negative-gray and negative-neutral, showed significant/marginally significant correlations between reaction time and right medial prefrontal ( $r = 0.713/0.755$ ;  $P = 0.047/0.069$ ) and right motor ( $r = 0.677/0.874$ ;  $P = 0.013/0.096$ ) cortical activation signals.

Reaction time in negative emotions correlated significantly ( $r = 0.935/0.876$ ;  $P = 0.023/0.032$ ) with magnetic field strength (RMS/dipole RMS) in EMF, whereas no significant correlations were found with late magnetic fields (RF, MF, MEFI). No significant correlations between reaction times and magnetic fields were found in the other three conditions (positive, neutral, gray).

In summary, subjects showed significant correlations of reaction time with subjective experience, right medial prefrontal/motor cortical fMRI signals and early magnetic field strength only in negative emotions but neither in positive emotions nor in both control conditions (neutral, gray).

#### Discussion

The present study combined hemodynamic and electromag-

netic measurements to investigate spatiotemporal activation patterns in negative and positive emotional processing. The main findings are the following: (i) differences in orbitofrontal and lateral prefrontal cortical fMRI activation patterns between negative and positive emotional stimulation which both differed from non-emotional conditions (gray and neutral); (ii) early orbitofrontal magnetic fields and dipoles only in emotional but not in non-emotional conditions with differences in strength, localization and onset of dipoles between positive and negative emotions; (iii) significant correlation of reaction time with subjective ratings, right medial/motor cortical fMRI signals and early magnetic field in MEG only in negative emotional processing but neither in positive emotional condition nor in both control conditions.

The results of the present study confirm our initial hypothesis of spatial and temporal differences between negative and positive emotional processing from medial/lateral orbitofrontal to premotor/motor cortex, which, in addition, lend further support to the assumption of a functional subdivision of the orbitofrontal cortex into a medial and a lateral part showing distinct temporal and connective patterns. Negative and positive emotional processing led to almost inverse alterations (positively or negatively correlated activity) in medial and lateral orbitofrontal cortex, showed distinct temporal patterns, and could be characterized by differences in effective connectivity between medial and lateral prefrontal cortical structures. Consequently, negative and positive signification of somatic and cognitive events may be subserved by different prefrontal cortical neural networks, which can be distinguished by their spatial, temporal and connective properties.

### ***Spatial, Temporal and Connectional Differences in Orbitofrontal Cortex during Negative and Positive Emotional Processing***

In accordance with previous studies we found strong activation in orbitofrontal, lateral prefrontal and premotor cortex during emotional stimulation (Pardo *et al.*, 1993; George *et al.*, 1995; Morris *et al.*, 1996, 1998; Baker *et al.*, 1997; Imaizumi *et al.*, 1997; Irwin *et al.*, 1997; Lane *et al.*, 1997a,b,c; Paradiso *et al.*, 1997; Phillips *et al.*, 1997; Büchel *et al.*, 1998; LaBar *et al.*, 1998). Most studies report activation of different cortical regions during negative and positive emotional stimulation (George *et al.*, 1995; Morris *et al.*, 1996, 1998; Baker *et al.*, 1997; Imaizumi *et al.*, 1997; Irwin *et al.*, 1997; Lane *et al.*, 1997a,b,c; Lang *et al.*, 1998), whereas only some authors postulate similar neuro-anatomical substrates for negative and positive emotional processing in prefrontal cortex (Beauregard *et al.*, 1998) and/or amygdala (Breiter *et al.*, 1996, Phelps *et al.*, 1998).

We found dissimilar extents of activity in medial orbitofrontal and ventral lateral orbitofrontal cortex during negative and positive emotional processing (see Table 2). Similar to other authors, we found activation (i.e. positively correlated activity) in orbitofrontal cortex during negative emotional stimulation and in lateral prefrontal cortex during positive emotional stimulation (Pardo *et al.*, 1993; George *et al.*, 1995; Baker *et al.*, 1997; Irwin *et al.*, 1997; Paradiso *et al.*, 1997; Phillips *et al.*, 1997; Morris *et al.*, 1998; Mayberg *et al.*, 1999). In addition, we found a high proportion of negatively correlated activity in orbitofrontal cortex during positive emotional processing and in lateral prefrontal cortex during negative emotional stimulation, which, depending on the interpretation of negatively correlated activity (see Methodological limitations), would be in accordance with PET studies reporting increases and decreases of

activity in similar regions. Baker and co-workers (Baker *et al.*, 1997) found increased orbitofrontal and decreased lateral prefrontal cortical activity during negative emotional stimulation, which, with regard to orbitofrontal increase, is further supported by similar findings in other studies (George *et al.*, 1995; Paradiso *et al.*, 1997; Mayberg *et al.*, 1999). In contrast, positive emotional stimulation led to decreased orbitofrontal (Paradiso *et al.*, 1997) and increased lateral prefrontal (Baker *et al.*, 1997) cortical activity. Concerning laterality, we could not find any significant differences in right/left activation between negative and positive emotional processing in orbitofrontal cortex or in lateral prefrontal or other prefrontal cortical areas. Such a finding is in agreement with some studies (George *et al.*, 1995; Baker *et al.*, 1997; Gainotti *et al.*, 1997; Lane *et al.*, 1997a,b,c; Reimann *et al.*, 1997; Beauregard *et al.*, 1998), but it disagrees with other studies that find differential lateralization patterns in negative (right frontal cortex) and positive (left frontal cortex) emotions (Morris *et al.*, 1996, 1998; Imaizumi *et al.*, 1997; Irwin *et al.*, 1997; Paradiso *et al.*, 1997; Sutton *et al.*, 1997). In addition, we did not find any strong tendencies of lateralization of the early underlying dipole in MEG. However, due to the fact that the issue of lateralization in emotional processing cannot currently be resolved, interpretation of our finding of non-lateralization has to remain open.

Such spatial patterns in neural processing of negative and positive emotional stimulation are further underlined by consideration of temporal aspects as investigated with MEG. Similar to other authors (Kristeva *et al.*, 1991; Salmelin and Hari, 1994; Nagamine *et al.*, 1996; Hoshiyama *et al.*, 1997; Joliot *et al.*, 1998; Kristeva-Feige *et al.*, 1997, 1994; Stippich *et al.*, 1998), we found movement-related magnetic fields in all four conditions (i.e. which did not differ in the movement required) and, in addition, an EMF only in emotional (negative and positive) but not in non-emotional (neutral, gray) conditions. Since similar early changes in magnetic fields have never been observed in MEG studies investigating movements only (see above), such early magnetic activity must somehow be related to emotional processing, though other effects cannot be excluded entirely (see Methodological limitations). Similar to investigations with EEG (Naumann *et al.*, 1992, 1993; Cuthbert *et al.*, 1993; Pihan *et al.*, 1997; Schupp *et al.*, 1997; Aftanas *et al.*, 1998), magnetic activity differed considerably between negative and positive emotional conditions. In negative emotional stimulation, both the early magnetic field and its corresponding dipoles showed an earlier onset (-1700 ms), a higher strength and a more medially oriented orbitofrontal location than in the positive emotional condition, which was characterized by a later onset (-1200 ms), a lower strength and a rather laterally oriented orbitofrontal location (see Tables 3 and 4 as well as Figs 2 and 5). Such differences in magnetic fields are in accordance with results from fMRI where the orbitofrontal cortex was strongly activated in negative emotional stimulation and the lateral prefrontal cortex in positive emotional stimulation (see above).

Considering spatial and temporal differences during negative and positive emotional stimulation, one may thus assume distinct neural pathways in prefrontal cortex for negative and positive emotions. Negative emotional stimulation is processed early with strong activation from medial orbitofrontal cortex to premotor/motor cortex via the cingulate cortex. In contrast, prefrontal activation in positive emotional stimulation is generated later and weaker in lateral orbitofrontal and lateral prefrontal cortex continuing to premotor/motor cortex via cingulate cortex and medial prefrontal cortex. Such a differential



role of medial and lateral orbitofrontal cortex in negative and positive emotional processing is further supported by consideration of cytoarchitectonical, connectional and functional differences (Morecraft *et al.*, 1992; Bates and Goldman-Rakic, 1993; Carmichael and Price, 1994, 1995a,b, 1996; Barbas, 1995; Morecraft and Van Hoesen, 1998). The medial orbitofrontal cortex shows an agranular or dysgranular cytoarchitectonic; is connected with hippocampal formation, ventrolateral parts of the basal nucleus of the amygdala, dorsolateral prefrontal cortex (area 9 and rostral 46), dorsomedial parts of mediodorsal thalamic nucleus and anterior cingulate cortex; and is functionally involved in negative emotional processing and affective reactivity to alien stimuli (Morecraft *et al.*, 1992; Baker *et al.*, 1997; Drevets and Raichle, 1998; Morecraft and Van Hoesen, 1998). In contrast, the lateral orbitofrontal cortex shows a granular cytoarchitectonic, and is connected with ento/perirhinal cortex, ventromedial parts of the basal nucleus of amygdala, dorsolateral prefrontal cortex (area 45 and caudovernal 46), ventromedial parts of mediodorsal thalamic nucleus, premotor and parietal cortex, and posterior cingulate cortex. One may thus hypothesize that, functionally, the lateral orbitofrontal cortex may be related to the formation of associations between emotions and thoughts (Morecraft *et al.*, 1992; Bates and Goldman-Rakic, 1993; Baker *et al.*, 1997; Drevets and Raichle, 1998; Morecraft and Van Hoesen, 1998). Consequently, negative emotional stimulation may be processed in medial prefrontal cortical areas, whereas positive emotional stimulation uses lateral prefrontal cortical structures.

Such a functional dissociation between medial and lateral prefrontal cortex with distinct temporal properties is further supported by our analysis of structural connectivity in primate prefrontal cortex showing a clear connectional differentiation between medial and lateral prefrontal cortical pathways, which would be in full accordance with the present fMRI/MEG data as measured in humans. This distinction between medial and lateral prefrontal cortical pathways may account for the process of negative and positive signification of somatic and cognitive events. According to Damasio (Damasio, 1994, 1995, 1997), somatic and cognitive events become signified by emotions either negatively or positively before they are transformed into actions. The activation paradigm in the present study consisted in concomitant emotional (negative and positive visual pictures) and motor (finger extension with a mouse click after the appearance of each picture) stimulation, thus requiring transformation of negative and positive emotional experience into (motor) action, and therefore investigated the spatial and temporal course of emotional-motor activation from orbitofrontal to premotor/motor cortex via the various prefrontal cortical regions. Spatial and temporal differences between negative and positive emotional processing may be interpreted as a support for the assumption that the process of transformation of negatively and positively signified events into actions may be subserved by distinct prefrontal cortical networks.

### **Methodological Limitations**

(i) We applied several strategies to minimize arousal and attention effects; such influences cannot, however, be excluded entirely in our activation paradigm. Positive, negative and neutral pictures were matched for content, dominance and arousal (see Materials and Methods). Psychological states as measured with the Befindlichkeitskala (see Materials and Methods) and subjective evaluation of emotional pictures in our subjects did not differ from those of the respective normal

populations. Consequently, differences between conditions in fMRI/MEG signals can be accounted for neither by increased pre-experimental arousal nor by altered emotional perception/attention in our subjects. In order to exclude attentional/arousal effects related to switches between different conditions we eliminated all fMRI/MEG signals from analysis which were associated with the first and last picture within each block. In addition we included two non-emotional control conditions, gray and neutral pictures, to account for potential effects of arousal and attention by visual stimulation. If peculiarities were found only in an emotional (negative/positive versus neutral) condition but neither in neutral (i.e. gray-neutral) nor in gray (i.e. gray-negative/positive) conditions, such characteristics may be specifically related to emotional processing, whereas similar findings in both emotional and non-emotional conditions may rather indicate attentional/arousal effects; however, this is not the case in the present results. Nevertheless attention/arousal effects of particular scenes in IAPS, as for example in pictures with mutilated faces, cannot be excluded entirely, since we were unable to account for differences in attention/arousal between pictures within one condition. Moreover, due to the rather coarse categorization of emotions (only according to the valence; see above), we were unable to further distinguish between different kinds of negative emotional processing. For example, negative emotions may concern disgust, sadness or anxiety so that neither the distinct kinds of negative valences nor the distinct arousal/attention patterns associated respectively could be further specified and differentiated.

(ii) We did not investigate test-retest reliability, which due to fast habituation processes, as shown in a previous study (Breiter *et al.*, 1996; Büchel *et al.*, 1998; Whalen *et al.*, 1998), may methodologically be problematic anyway. In order to avoid habituation of emotional stimulation in fMRI and MEG, both investigations were undertaken in a random sequence and blocks were counterbalanced across fMRI/MEG investigations to avoid potential order effects.

(iii) Measurements in fMRI covered only the frontal lobe, whereas other regions of potential interest, e.g. the amygdala, were excluded from the analysis. We used rather slow but silent sequences in fMRI in order to avoid further additional stress as well as interference with emotional stress. In addition, the main purpose of the present study was to investigate spatial and temporal processing of negative and positive emotional processing in prefrontal cortex to give further empirical support to Damasio's hypothesis of the importance of emotions in relation to action. We therefore focused particularly on the functional relationships between orbitofrontal and premotor/motor cortex using an activation paradigm with concomitant emotional and motor stimulation. However, functional connectivity within the prefrontal cortex as well as functional connections between amygdala and orbitofrontal cortex should be investigated in a separate study. The orbitofrontal cortex is close to regions with a high potential for magnetic susceptibility artifact. Given the unpredictable effects on  $T_2$ -weighted signal change from regions with high susceptibility we, in agreement with Breiter and co-workers (Breiter *et al.*, 1996, 1997), checked and confirmed that activations seen in our experiment did not overlap regions of susceptibility artifact on the functional images; otherwise (i.e. if the artifact was as high as or even higher than the stimulus-correlated activity) they were excluded from the analysis. We included only stimulus-correlated variation in signal intensity which is more or less independent of overall signal intensity. In addition, susceptibility artifacts may reduce

detection of stimulus-correlated variation in signal intensity which supports the assumption that orbitofrontal activity, as detected in negative emotions, could not be accounted for by artifacts. Even if we cannot exclude entirely differences in signal-noise ratios between different regions, we nevertheless compared standard deviations of activity between orbitofrontal cortex and the other ROIs. Orbitofrontal activity showed no higher standard deviations than other regions (see Table 1) so that there seems to be no major difference in this regard.

(iv) We found a high proportion of negatively correlated activity in fMRI; this activity can be interpreted in several ways. Negatively correlated activity in fMRI, which was particularly strong in negative emotions, could reflect a decrease of neuronal activity with neural inhibition in the activation condition, an increase of neuronal activity in the control condition, a 'steal effect' of regional cerebral blood flow (rCBF), or an altered coupling mechanism between oxygen consumption and rCBF (Leschinger *et al.*, 1999). Several PET studies found concomitant increases and decreases in rCBF during emotional stimulation (George *et al.*, 1995; Baker *et al.*, 1997; Lane *et al.*, 1997a,b,c; Paradiso *et al.*, 1997; Reimann *et al.*, 1997; Drevets and Raichle, 1998), so that it seems quite plausible, at least in the present study, to relate such negatively correlated voxels to decreased regional activity in either of the two conditions within the respective contrast. Even if similar regions are involved, their pattern of increased and decreased activity (i.e. positively and negatively correlated activity) may nevertheless differ between two conditions as is apparently the case in negative and positive emotional stimulation (see Table 2). Regions that are activated during negative emotional processing, e.g. the orbitofrontal cortex, may be suppressed (or deactivated) in positive emotional processing and vice versa (Drevets and Raichle, 1998; Mayberg *et al.*, 1999). For example, deactivation in orbitofrontal cortex, as observed in positive emotional stimulation, could be closely related to inhibition of affective associations in relation to visual stimuli (Dias *et al.*, 1997), which, in our case, may be interpreted as a suppression of negative emotional processing. Finally, although it can never be fully excluded, it seems rather unlikely that our finding of negatively correlated activity reflects only 'noise' since we applied different thresholds (see Materials and Methods) and, in addition, 'noise' would not occur with such a differential pattern across different regions in different conditions.

(v) We did not explicitly investigate visual attentional functions which could be related to EMFs. However, our findings of considerable differences in strength of EMFs between negative and neutral emotion pictures makes such an explanation rather unlikely since both kind of pictures differed only in emotional valence but neither in dominance nor in arousal (see Materials and Methods). Eye movements cannot account for EMF since EOG was measured in MEG (but not in fMRI; see Materials and Methods) with rejection of contaminated electromagnetic signals so that electro-ocular artifacts were excluded from analysis. In addition, all subjects had to fixate a central point during presentation of each picture in MEG and fMRI in order to avoid eye movements. Furthermore, as has been shown in fMRI (Darby *et al.*, 1996; Bodis-Wollner *et al.*, 1997), eye movements would rather lead to activation in superior medial prefrontal cortex (area 6, 8) than inferior prefrontal and orbitofrontal cortex as in emotional processing; hence it seems unlikely that orbitofrontal and inferior prefrontal activation, as observed in the present study, is related to eye movements. However, we were unable to control the mode and intensity of visual scanning

(unrelated to eye movements) during presentation of pictures which may differ between negative and positive emotional processing.

## Conclusions

The role of medial and lateral orbitofrontal cortex, as well as temporal properties of prefrontal cortical activation during negative and positive emotional stimulation, remains unclear. According to Damasio, negatively and positively signified events may be transformed into action using distinct prefrontal cortical networks. We therefore investigated spatiotemporal activation patterns in orbitofrontal and prefrontal cortex during concomitant emotional-motor stimulation in a combined MEG/fMRI study.

Negative emotional processing could be characterized by increased orbitofrontal activation and early (-1700 ms), strong and more medially oriented orbitofrontal dipoles, whereas positive emotional stimulation led to lateral prefrontal activation with later (-1500 ms), weaker and more laterally oriented orbito/prefrontal dipoles.

It is concluded that negative emotional processing can be characterized by early and strong medial orbitofrontal cortical activation, whereas positive emotional processing generates later and weaker activation in lateral orbitofrontal and lateral prefrontal cortex. Thus the present results confirm the assumption of a functional dissociation between medial and lateral orbitofrontal cortex in negative and positive emotional processing. In addition, negatively and positively signified events may be transformed into action using distinct, i.e. medial and lateral prefrontal, cortical networks.

## Notes

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## References

- Adolphs R, Tranel D, Damasio AR (1998) The human amygdala in social judgement. *Nature* 393:470-474.
- Aftanas L, Lotova N, Koshkarov V, Makhnev V, Mordvintsev Y, Popov S (1998) Non-linear dynamic complexity of the human EEG during evoked emotions.
- Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS (1993) Processing strategies for time-course data sets in functional MRI of the human brain. *Magn Res Med* 30:161-173.
- Baker SC, Frith CD, Dolan RJ (1997) The interaction between mood and cognitive function studied with PET. *Psychol Med* 27:565-578.
- Barbas H (1995) Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. *Neurosci Biobehav Rev* 19:499-510.
- Bates J, Goldman-Rakic PS (1993) Prefrontal connections of medial motor areas in rhesus monkey. *J Comp Neurol* 336:211-228.
- Beauregard M, Karama S, Leroux JM, Lecours AR, Beaudoin G, Bourgouin P (1998) The functional neuroanatomy of amusement, disgust and sexual arousal. *NeuroImage* 7:5909.
- Bodis-Wollner I, Bucher SF, Seelos KC, Paulus W, Reiger M, Oertel W (1997) Functional MRI mapping of occipital and frontal cortical activity during voluntary and imagined saccades. *Neurology* 49:416-420.
- Breiter HC, Etcoff N, Whalen PJ, Kennedy WA, Rauch S, Buckner RL, Strauss M, Hyman SE, Rosen BR (1996) Response and habituation of

- the human amygdala during visual processing of facial expression. *Neuron* 17:875–887.
- Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew T, Rosen BR, Hyman SE (1997) Acute effects of cocaine on human brain activity and emotion. *Neuron* 19:591–611.
- Büchel C, Friston KJ (1997) Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. *Cereb Cortex* 7:768–778.
- Büchel C, Morris J, Dolan RJ, Friston KJ (1998) Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* 20:947–957.
- Bullmore ET, Horwitz B, Morris RG, Curtis YA, McGuire PK, Sharma T, Williams SCR, Murray RM, Brammer MJ (1998) Causally connected cortical networks for language in functional MRI images of normal and schizophrenic subjects. *NeuroImage* 784:S204.
- Cabeza R, McIntosh A, Tulving E, Nyberg L, Grandy C (1997) Age-related differences in effective neural connectivity during encoding and recall. *NeuroReport* 8:3479–3483.
- Carmichael ST, Price JL (1994) Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *J Comp Neurol* 346:366–402.
- Carmichael ST, Price JL (1995a) Limbic connections of the orbital and medial prefrontal cortex of macaque monkeys. *J Comp Neurol* 363:615–641.
- Carmichael ST, Price JL (1995b) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *J Comp Neurol* 363:642–664.
- Carmichael ST, Price JL (1996) Connectional networks within the orbital and medial prefrontal cortex of macaque monkey. *J Comp Neurol* 371:179–207.
- Cuthbert B, Bradley MM, Lang PJ (1993) Orienting and affect: cortex–reflex connection. *Psychophysiology* 30(Suppl):57.
- Damasio AR (1994) *Descartes's error: emotion, reason, and the human brain*. New York: Grosset/Putnam.
- Damasio AR (1995) On some functions of the human prefrontal cortex. *Ann NY Acad Sci* 769:241–251.
- Damasio AR (1997) Towards a neuropathology of emotion and mood. *Nature* 386:769–770.
- Darby DG, Nobre A, Thangaraj V, Edelman R, Mesulam M, Warach S (1996) Cortical activation in the human brain during lateral saccades using EPSTAR functional magnetic resonance imaging. *NeuroImage* 3:53–62.
- Davis M, Rainnie Cassell M (1994) Neurotransmission in the rat amygdala related to fear and anxiety. *Trends Neurosci* 17:208–214.
- Dias R, Robbins TW, Roberts AC (1997) Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sorting Test: restriction to novel situations and independence from 'on-line' processing. *J Neurosci* 17:9285–9297.
- Drevets WC, Raichle ME (1998) Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. *Cogn Emot* 12:353–385.
- Gaschler-Markewski B, Baumgart F, Tempelmann C, Schindler F, Stiller D, Heinze HJ, Scheich H (1997) Statistical methods in functional magnetic resonance imaging with respect to non-stationary time series: auditory cortex activity. *Magn Res Med* (in press).
- Gainotti G, Azzoni A, Gasparini F, Marra C, Razzano C (1997) Relation of lesion location to verbal and nonverbal mood measures in stroke patients. *Stroke* 28:2145–2149.
- George MS, Ketter T, Parekh P, Horwitz B, Herscovitch P, Post R (1995) Brain activity during transient sadness and happiness in healthy women. *Am J Psychiat* 152:341–351.
- Hamm AO, Vaitl D (1993) Emotionsinduktion durch visuelle Reize: Validierung einer Stimulationsmethode auf drei Reaktionsebenen. *Psychol Runds* 44:143–161.
- Heinze HJ, Mangun GR, Burchert W, Hinrichs H, Scholz M, Munte TF, Gos A, Scherg M, Johannes S, Hundeshagen H, Gazzaniga MS, Hillyard SA (1994) Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature* 372:543–546.
- Hoshiyama M, Kakigi R, Berg P, Koyama S, Kitamura Y, Shimojo M, Watanabe S, Nakamura A (1997) Identification of motor and sensory brain activities during unilateral finger movement: spatiotemporal source analysis of movement-associated magnetic fields. *Exp Brain Res* 115:6–14.
- Hyman S (1998) A new image for fear and emotion. *Science* 393:417–418.
- Imazumi S, Mori K, Kiritani S, Kawashima R, Sugiura M, Fukuda H, Itoh K, Kato T, Nakamura A, Hatano K, Kojima S, Nakamura K (1997) Vocal identification of speaker and emotion activates different brain regions. *NeuroReport* 8:2809–12.
- Irwin W, Davidson RJ, Lowe MJ, Mock BJ, Sorenson JA, Turski PA (1996) Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *NeuroReport* 7:1765–1769.
- Irwin W, Mock BJ, Sutton SK, Orendi JL, Sorenson JA, Turski PA, Kalin NH, Davidson RJ (1997) Positive and negative affective responses: Neural circuitry revealed using fMRI. *Soc Neurosci Abstr* 23:1318.
- Irwin W, Mock BJ, Sutton SK, Anderle M, Kalin NH, Sorenson JA, Turski PA, Davidson RJ (1998) Ratings of affective stimulus characteristics and measures of affective reactivity predict MR signal change in the human amygdala. *NeuroImage* 7:908.
- Joliot M, Crivello F, Badier JM, Diallo B, Tzourio N, Mazoyer B (1998) Anatomical congruence of metabolic and electromagnetic activation signals during a self-paced motor task: a combined PET-MEG study. *NeuroImage* 7:337–351.
- Kammer T, Bellemann M, Gückel F, Brix G, Gass A, Schlemmer H, Spitzer Mb (1997) Functional MR imaging of the prefrontal cortex: specific activation in a working memory task. *Magn Reson Imag* 15:879–889.
- Kristeva R, Cheyne D, Deecke L (1991) Neuromagnetic fields accompanying unilateral and bilateral voluntary movements: topography and analysis of cortical sources. *Electroenceph Clin Neurophysiol* 81:284–298.
- Kristeva-Feige R, Walter H, Lütkenhöner B, Hampson S, Ross B, Knorr U, Steinmetz H, Cheyne D (1994) A neuromagnetic study of the functional organisation of the sensorimotor cortex. *Eur J Neurosci* 6:532–539.
- Kristeva-Feige R, Rossi S, Feige B, Mergner T, Lücking C, Rossini PM (1997) The Bereitschaftspotential paradigm in investigating voluntary movement organization in human using magnetoencephalography. *Brain Res Prot* 1:13–22.
- LaBar KS, Gatenby C, Gore J, LeDoux JE, Phelps E (1998) Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron* 20:937–945.
- Lane RD, Fink GR, Chau PM, Dolan RJ (1997a) Neural activation during selective attention to subjective emotional responses. *NeuroReport* 8:3969–3972.
- Lane RD, Reimann EM, Ahern GL, Schwartz GE, Davidson RJ (1997b) Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiat* 154:926–933.
- Lane RD, Reimann EM, Bradley M, Lang PJ, Attern GL, Davidson RJ, Schwartz GE (1997c) Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* 35:1437–1444.
- Lang PJ (1980) Self-assessment manikin. Gainesville, FL: The Center for Research in Psychophysiology, University of Florida.
- Lang PJ, Bradley MM, Cuthbert BN (1997) International Affective Picture System (IAPS): technical manual and affective ratings. Gainesville: The Center for Research in Psychophysiology, University of Florida.
- Lang PJ, Bradley MM, Fitzsimmons JR, Cuthbert BN, Scott JD, Moulder B, Nangia V (1998) Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology* 35:199–210.
- Leschinger A, Baumgart F, Gaschler-Markewski B, Northoff G, Scheich H, Bogerts B (1999) Effect of training and experience on task performance and prefrontal cortical activation during an auditory working memory task. *Hum Brain Map* (in press).
- Mayberg H, Liotti M, Brannan S, McGinnis S, Mahurin R, Jerabek P, Silva J, Tekell J, Martin C, Lancaster J, Fox P (1999) Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *Am J Psychiat* 156:675–682.
- McIntosh AR, Gonzalez-Lima F (1994) Structural equation modeling and its application to network analysis of functional brain imaging. *Hum Brain Map* 2:2–22.
- McIntosh AR, Grady GL, Haxby JV, Ungerleider LG, Horwitz B (1996) Changes in limbic and prefrontal functional interactions in a working memory task for faces. *Cereb Cortex* 6:571–584.
- Morecraft RJ, Geula C, Mesulam M (1992) Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. *J Comp Neurol* 323:341–358.
- Morecraft RJ, Van Hoesen G (1998) Convergence of limbic input to the cingulate motor cortex in the rhesus monkey. *Brain Res Bull* 45:209–232.
- Morris JS, Friston KJ, Büchel C, Frith CD, Young AW, Calder AJ, Dolan RJ



- (1998) A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* 121:47–57.
- Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, Dolan RJ (1996) A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* 383: 812–815.
- Nagamine T, Kajola M, Salmelin R, Shibasaki H, Hari R (1996) Movement-related slow cortical magnetic fields and changes of spontaneous MEG and EEG brain rhythms. *Electroenceph Clin Neurophysiol* 99:274–286.
- Naito E, Kinomura S, Kawashima R, Geyer S, Zilles K, Roland PE (1998) Correlation of the rCBF in anterior cingulate cortex with reaction time. *NeuroImage* 7:8948.
- Naumann E, Bartussek D, Diedrich O, Laufer E (1992) Assessing cognitive and affective information processing functions of the brain by means of the late positive complex of the event-related potential. *J Psychophysiol* 6:285–298.
- Naumann E, Bartussek D, Diedrich O, Vogelbacher D, Mehrtens S (1993) Emotionality and the late positive complex of the event-related potential. In: New development in event-related potentials (Heinze HJ, Münte TF, Mangun GR, eds). Boston, MA: Birkhäuser.
- Paradiso S, Johnson DL, Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Ponto LLB, Watkins GL, Hichwa RD (1997) Left amygdala and prefrontal activation during conscious evaluation of emotional valence of visual stimuli. *NeuroImage* 5:S116.
- Paradiso S, Robinson RG, Andreasen NC, Downhill JE, Davidson RJ, Kirchner PT, Watkins L, Ponto L, Hichwa RD (1997) Emotional activation of limbic circuitry in elderly normal subjects in a PET study. *Am J Psychiat* 154:384–389.
- Pardo J, Pardo PJ, Raichle ME (1993) Neural correlates of self-induced dysphoria. *Am J Psychiat* 150:713–719.
- Pihan H, Altenmüller E, Ackermann H (1997) The cortical processing of perceived emotion: a DC potential on affective speech prosody. *NeuroReport* 8:623–627.
- Phelps EA, LaBar KS, Gatenby JC, O'Connor KJ, Gore JC (1998) fMRI of amygdala activation related to positive and negative emotional scenes. *NeuroImage* 7:S899.
- Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, Perrett DI, Rowland D, Williams SCR, Gray JA, David AS (1997) A specific neural substrate for perceiving facial expressions of disgust. *Nature* 389:495–498.
- Reimann EM, Lane RD, Ahern G, Schwartz G, Davidson RJ, Friston KJ, Yun L, Chen K (1997) Neuroanatomical correlates of externally and internally generated emotions. *Am J Psychiat* 154:918–925.
- Salmelin R, Hari R (1994) Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movements. *Neuroscience* 60:537–550.
- Sanders JA, Lewine JD, and Orrison WW (1996) Comparison of primary motor cortex localization using functional magnetic resonance imaging and magnetoencephalography. *Hum Brain Map* 4:47–57.
- Schneider F, Gur RE, Mozley L, Smith RJ, Mozley P, censits DM, Alavi A, Gur R (1995) Mood effects on limbic blood flow correlate with emotional self-rating: a PET study with oxygen-15 labeled water. *Psychiat Res Neuroimag* 61:265–283.
- Schupp H, Cuthbert B, Bradley M, Birbaumer N, Lang P (1997) Probe P3 and blinks: two measures of affective startle modulation. *Psychophysiology*, 34:1–7.
- Stephan KE, Kötter R (1998) A formal approach to the translation of cortical maps. In: International School of Biophysics: neural circuit and networks, NATO ASI Series F (Torre V, Nicholis J, eds), pp. 205–226. Berlin: Springer Verlag.
- Stephan KE, Kötter R (1999) One brain – many maps: an introduction to coordinate-independent mapping by Objective Relational Transformation (Ort). *Neurocomputing* 26:1049–1054.
- Stephan KE, Zilles K, Kötter R (2000) Coordinate-independent mapping of structural and functional data by Objective Relational Transformation (ORT). *Phil Trans R Soc Lond B* (in press).
- Stippich C, Freitag P, Kassubek J, Sörös P, Kamada K, Kober H, Scheffler K, Hopfengärtner R, Bilecen D, Radü E, Vieth J (1998) Motor, somatosensory and auditory cortex localization by FMR and MEG. *NeuroReport* 9:1953–1957.
- Sutton SK, Davidson RJ, Donzella B, Irwin W, Dotts DA (1997) Manipulating affective states during extended picture presentation. *Psychophysiology* 34:217–226.
- Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme Verlag.
- Walker EA (1940) A cytoarchitectural study of the prefrontal area of Macaque monkey. *J Comp Neurology* 73:59–86.
- Whalen PJ, Rauch SL, Etkoff NL, McInerney SC, Lee MB, Jenike MA (1998) Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 18:411–418.
- Zerssen D.v. (1976) Die Befindlichkeitsskala. Weinheim: Beltz.
- Young MP, Scannell JW, O'Neill MA, Hilgetag CC, Burns G, Blakemore C (1995) Non-metric multidimensional scaling in the analysis of neuroanatomical connection data and the organization of the primate cortical visual system. *Phil Trans R Soc Lond B* 34.