◆ **Human Brain Mapping 21:202–212(2004)** ◆

Reciprocal Modulation and Attenuation in the Prefrontal Cortex: An fMRI Study on Emotional–Cognitive Interaction

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Abstract: Everyday and clinical experience demonstrate strong interactions between emotions and cognitions. Nevertheless the neural correlates underlying emotional–cognitive interaction remain unclear. Using event-related fMRI, we investigated BOLD-signal increases and decreases in medial and lateral prefrontal cortical regions during emotional and non-emotional judgment of photographs taken from the International Affective Picture System (IAPS). Emotional and non-emotional judgment conditions were compared to each other as well as with baseline allowing for distinction between relative signal changes (comparison between conditions) and true signal changes (referring to baseline). We have found that: (1) both emotional and non-emotional judgment of IAPS pictures were characterized by signal increases in ventrally and dorsally located lateral prefrontal cortical areas and concurrent signal decreases in ventro- and dorsomedial prefrontal cortex; (2) direct comparison between emotional and non-emotional judgment showed relative signal increases in ventro- and dorsomedial prefrontal cortex, and in contrast, relative signal increases were detected in ventrally and dorsally located lateral prefrontal cortical areas when comparing non-emotional to emotional judgment; and (3) as shown in separate comparisons with baseline, these relative signal changes were due to smaller signal decreases in ventro- and dorsomedial prefrontal cortex and smaller signal increases in ventrally and dorsally located lateral prefrontal cortical areas during emotional judgment. Therefore, the emotional load of a cognitive task lead to both less deactivation of medial prefrontal regions and, at the same time, less activation of lateral prefrontal regions. Analogous patterns of reciprocal modulation and attenuation have previously been described for other cortical regions such as visual and auditory areas. Reciprocal modulation and attenuation in medial and lateral prefrontal cortex might constitute the neurophysiologic basis for emotional–cognitive interaction as observed in both healthy and psychiatric subjects. *Hum. Brain Mapp. 21:202–212, 2004.* © 2004 Wiley-Liss, Inc.

Key words: emotion; cognition; judgment; baseline; deactivation; attenuation; medial prefrontal cortex; lateral prefrontal cortex

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Contract grant sponsor: Sachsen-Anhalt; Contract grant sponsor: NIMH; Contract grant number: RO1MH57980, RO1MH60734; Contract grant sponsor: NARSAD; Contract grant sponsor: DAAD; Contract grant number: D/02/46858; Contract grant sponsor: DFG; Contract grant number: 304/4-1.

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Received for publication 24 June 2003; Accepted 5 November 2003

DOI 10.1002/hbm.20002

INTRODUCTION

One of the most pertinent questions in cognitive neuroscience is the relationship between emotions and cognitions. We experience strong emotional influences on our cognitions, which might be reflected in attention shift deficits of depressive patients. Attention-demanding cognitive tasks may influence the intensity of our emotional experience, which is made use of in cognitive–behavioral therapy of anxiety disorders and depression. It seems, therefore, that emotional states can influence cognitive task performance and vice-versa. Neural correlates and functional mechanisms underlying these interactions remain unclear. Lesion and functional imaging studies have predominantly related emotional processing to medial prefrontal cortical regions, such as the ventro- and dorsomedial prefrontal cortex (VMPFC, DMPFC) as well as the medial orbitofrontal cortex (MOFC) [Damasio, 1999; Davidson and Irwin, 1999; Northoff et al., 2000, 2002; Phan et al., 2002]. In contrast, cognitive tasks have been implicated in the activation of lateral prefrontal cortical regions, such as the ventro- and dorsolateral prefrontal cortex (VLPFC, DLPFC) and adjacent lateral prefrontal cortical regions [see Duncan and Owen, 2000 for an overview].

A few studies have investigated the influence of emotion (as induced by photographs, video presentation, or music) on different cognitive tasks, such as a working memory task [Perlstein et al., 2002], an attention-demanding task [Simpson et al., 2000], a Go–NoGo task [Elliott et al., 2000] and a verbal fluency task [Baker et al., 1997]. Compared to neutral stimuli, emotional stimuli were associated with larger signal increases in medial prefrontal cortical regions (e.g., VMPFC, DMPFC) and smaller signal increases in lateral prefrontal cortical regions (e.g., VLPFC, DLPFC) during the respective cognitive tasks.

Fewer studies have directly addressed the cognitive modulation of emotional processing: Gusnard et al., [2001] examined cognitive influences on emotional processing by varying the cognitive task related to emotional photographs. Subjects had to perform two types of judgment task (emotional: pleasant vs. unpleasant; non-emotional: indoors vs. outdoors) in response to emotional stimuli. The emotional judgment was associated with activity increases in the DMPFC compared to the non-emotional judgment. Similarly, Lange et al., [2003] varied the cognitive task related to fearful faces. They observed signal increases in right VLPFC during a gender-decision task compared to an emotionality judgment task. Extending these findings, Keightley et al., [2003] varied the judgment task related to emotional photographs and faces. They found smaller ventral prefrontal activity when more attention was required for the task. At the same time, dorsal prefrontal regions were more active.

Based on the above-mentioned findings, we hypothesized a reciprocal modulation and attenuation of neural activity in medial and lateral prefrontal cortical regions. Reciprocal modulation can be defined by signal changes in opposite directions (i.e., signal increases and decreases) in different regions. Whereas emotional processing is known to lead to signal increases in medial prefrontal cortical regions and concurrent signal decreases in lateral prefrontal cortex, cognitive tasks may induce the reverse pattern with signal increases in lateral prefrontal cortex and signal decreases in medial prefrontal cortex. Emotional–cognitive interaction might then be associated with the functional mechanism of reciprocal attenuation. Inclusion of an emotional component into a cognitive task might lead to smaller signal decreases in medial prefrontal cortical regions and, at the same time, smaller signal increases in lateral prefrontal cortical regions. This means that in the emotional condition the signals might be closer to baseline in both medial and lateral prefrontal cortical regions that shall be called attenuation. Because attenuation is expected to concern both medial and lateral prefrontal cortical regions in opposite directions (i.e., smaller signal decreases or increases, respectively), we speak of reciprocal attenuation.

Although such reciprocal modulation and attenuation has not been reported yet in the case of the medial and lateral prefrontal cortex, analogous patterns have been observed in other cortical regions. In various regions such as right and left motor cortex [Allison et al., 2000], striate and extrastriate visual cortex [Kleinschmidt et al., 1998], subgenual anterior cingulate and right prefrontal cortex [Liotti et al., 2002; Mayberg et al., 1999], sub/pre- and supragenual anterior cingulate [Bush et al., 2000] as well as visual and auditory cortex [Laurienti et al., 2002], concurrent activation and deactivation has been demonstrated to be crucial for functional regulation and balance.

We used functional magnetic resonance imaging (fMRI) to test the hypothesis of reciprocal modulation and attenuation across medial and lateral prefrontal cortex during emotional–cognitive interaction. To induce emotional–cognitive interaction, we used an experimental design that required emotional and non-emotional judgments of both emotional and non-emotional photographs of the International Affective Picture System (IAPS). Investigation of reciprocal modulation and attenuation required differentiation between signal increases and decreases relative to baseline allowing for distinction between relative signal changes (between conditions) and true signal changes (referring to baseline) [Newman et al., 2001; Stark and Squire, 2001]. For this purpose trials were randomly ordered in an event-related design and separated by sustained baseline periods of variable and randomized duration.

SUBJECTS AND METHODS

Subjects

We studied 13 healthy subjects (3 women, 10 men; average age: 27.0, range: 23–34 years) without any psychiatric, neurologic, or medical disease. They all had at least 16 years of education with achievement of a college degree. All 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.

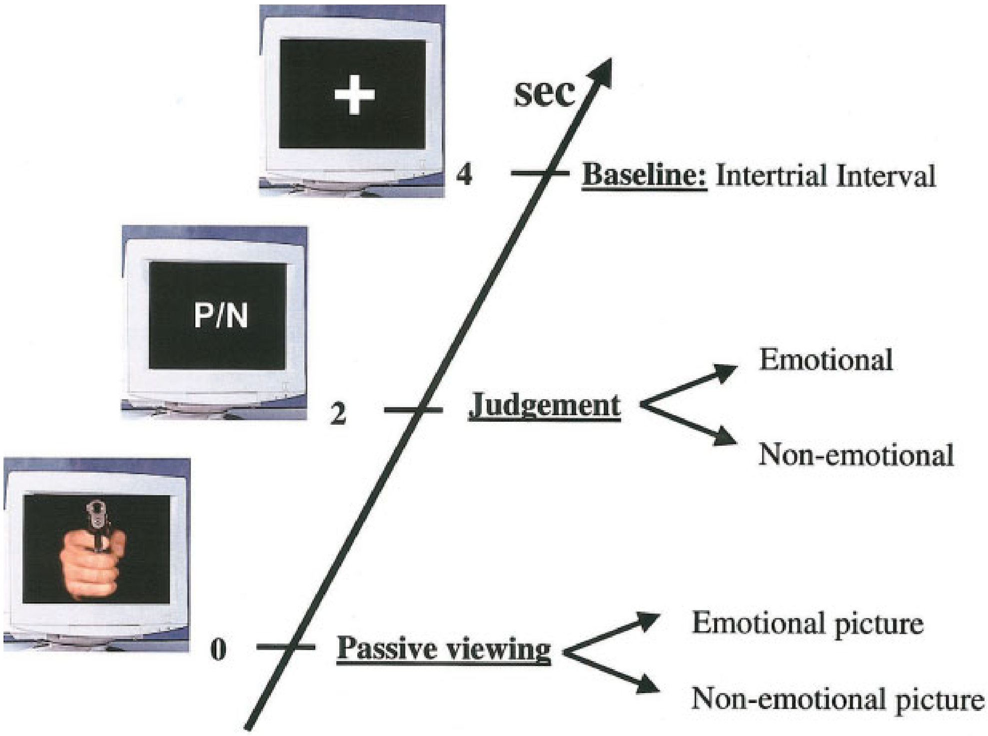

Figure 1.

Activation paradigm for emotional and non-emotional judgment of IAPS pictures. Passive viewing: presentation of emotional (positive, negative) or non-emotional (neutral) pictures taken from the International Affective Picture System (IAPS) for a duration of 2 sec. Judgment: emotional (P/N, F/A) or non-emotional (V/H) judgment task referring to the preceding picture. Response given by button click within 2 sec. Baseline: presentation of a fixation cross for variable durations (4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0 sec). An event included one IAPS picture (2 sec), appendant judgment task (2 sec), and subsequent fixation cross (4.0–8.0 sec). Four runs with 70 events each (a total of 280 events) were presented.

Paradigm

Subjects were asked to judge photographs taken from the International Affective Picture System (IAPS) [Center for the Study of Emotion and Attention, 1999]. Negative (valence: 1–3), positive (valence: 7–9), and neutral (valence: 4–6) pictures were presented for a duration of 2 sec. Picture sets were counterbalanced across subjects as well as within each subject according to the three categories: positive, negative, and neutral. Presentation of an IAPS picture was followed by the judgment task, which was indicated by a screen presented for the duration of 2 sec (Fig. 1). Three types of judgment task were distinguished: two emotional judgment tasks and one non-emotional judgment task. In one emotional task subjects had to judge whether an IAPS picture had a positive or negative emotional content (P/N). In the other emotional task, subjects had to judge whether feeling (i.e., awareness of emotional experience) had been present or absent during the picture presentation (i.e., feeling/absent feeling [F/A]). In contrast, the non-emotional judgment task concerned the format (i.e., portrait/landscape format = vertical/horizontal [V/H]) of the picture. 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. Because the three types of judgment task were presented in a randomized order, subjects were unable to anticipate the type of judgment task. The response was given by pressing a button (right thumb for P/F/V, left thumb for N/A/H). Reaction times were measured.

Each trial consisted of (1) the presentation of an IAPS photograph that could be emotional or non-emotional in content (per IAPS rating); (2) presentation of an instruction screen requesting a given judgment (that could be emotional or non-emotional); and (3) the pushing of the response button with right or left hand. Between trials a fixation cross in dark color was presented in the middle of the screen. This fixation cross served as baseline condition [Newman et al., 2001; Stark and Squire, 2001]. The baseline duration was randomly varied between 4–8 sec (4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0 sec) accounting for variable stimulus onset asynchrony. A total of 280 trials (each including picture viewing, judgment task and fixation cross) were presented in four runs (93 trials of each emotional condition and 94 trials of the non-emotional condition). The different types of IAPS pictures and judgment tasks were pseudo randomized within and across the four runs as well as among each other. Accordingly, during presentation of the picture, subjects did not know what type of judgment had to be given subsequently.

We are aware that the emotional and non-emotional judgment tasks used in this study might differ from each other in more than the emotional component. For example, the emotional judgment tasks might be associated with a higher level of conflict or difficulty than the non-emotional judgment task. Reaction times showed no differences between both types of judgment tasks, hence arguing against different levels of conflict or difficulty. Even if emotional judgments differed in that respect, higher levels of conflict or difficulty would probably increase the emotional involvement thus intensifying the emotional component rather than undermining it.

Before the experimental session subjects were familiarized with the paradigm by completing a test run with 20 trials.

During fMRI, pictures were projected automatically via a computer and a forward projection system on a screen placed at the end of the subject's gurney. Subjects lay supine in the scanner and viewed the screen through a mirror positioned on the head coil. Subjects were asked to keep their eyes open and fixate the middle of the screen in front of them. They were asked not to move finger, head, or body during the judgment tasks with the exception of the button press for the response.

Behavioral Monitoring

We measured reaction times that were defined as the time between the onset of the judgment screen and the subsequent button press. Reaction time was calculated separately for emotional and non-emotional judgments. Average reaction times were compared using paired *t*-tests. Subjective assessments of valence, dominance, and arousal of IAPS pictures were obtained from all subjects in a final session (after fMRI) using the self-assessment manikin [Lang et al., 1999]. The values did not differ from the ones obtained in a large population [Lang et al., 1999]. Psychological state before and after the fMRI investigation was assessed with the State Trait Anxiety Inventory (STAI) showing no significant differences in paired *t*-tests between the two time points.

Scanning Procedures

Scanning was carried out on a 1.5 T Siemens Vision (Erlangen, Germany). A gradient-echo T2* weighted echo-planar MR sequence was used for fMRI with the following parameters: TE (echo time) = 50 msec, FOV (field of view) = 240 cm, matrix = 64 × 64 interpolated to 128 × 128, voxel size: $4 \times 4 \times 6$ mm^3. Using a midsagittal scout image, we acquired 18 contiguous axial slices parallel to the anterior–posterior commissure (AC–PC) plane covering the entire brain in <2 sec. The first three acquisitions were discarded due to T1-saturation effects. Before 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.

TABLE I. Signal increases and decreases in prefrontal-cortex during judgment of IAPS pictures

	Judge > base: signal increases		Base > judge: signal decreases	
Brain region	*x, y, z**	*Z***	*x, y, z**	*Z***
VMPFC	—	—	4, 6, 56	4.43
DMPFC	—	—	20, 38, 42	4.00
rVLPFC	44, 46, 6	4.06	—	—
	40, 43, 15	3.21		
IVLPFC	−34, 52, 6	3.26	—	—
r(d)LPFC	44, 8, 24	4.90	—	—
l(d)LPFC	−54, 8, 26	4.90	—	—

Note opposite pattern of signal increases and decreases in medial (decreased) and lateral (increased) prefrontal cortical regions in judgment conditions.

* Montreal Neurological Institute coordinates given by *x, y, z* (in mm). Coordinates describe right(+)/left(−) (*x*), anterior(+)/posterior(−) (*y*), and superior(+)/inferior(−) distances (*z*).

** *Z*-score for maximal changes of foci within the respective region. Only foci with $Z > 3.23$ ($P < 0.001$ uncorrected, voxel level; $P < 0.05$, cluster level) were considered.

VMPFC, ventromedial prefrontal cortex (PFC); DMPFC, dorsomedial PFC; rVLPFC, right ventrolateral PFC; IVLPFC, left ventrolateral PFC; r and l(d)LPFC, right and left dorsally located lateral PFC regions (including dorsolateral PFC and dorsal parts of the inferior frontal gyrus).

Image Analyses

Image processing and statistical analyses were carried out using SPM99 software. 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. Voxels associated with movement conditions were searched for using the general linear model approach for time-series data suggested by Friston et al., [1995]. The anatomic localization and the stereotactic coordinates of local maxima were determined by reference to the MNI brain as provided by SPM.

We defined a design matrix modeling all three judgment tasks (P/N, F/A, V/H) as separate events. For fMRI group analyses, images of all subjects were analyzed in one design matrix, generating a random-effects model, allowing inference to the general population. Data were analyzed with respect to emotional and non-emotional judgment to account for emotional–cognitive interaction. In a first step, all three judgment tasks were pooled and compared to baseline (judgment task vs. baseline and baseline vs. judgment task) to show the neural correlates of judgment task in general. Both emotional judgment tasks (P/N, F/A) were compared to each other. Because this comparison showed no significant differences on either level of significance ($P < 0.0001$, $P < 0.001$, $P < 0.01$) these two judgment tasks were subsumed under emotional judgment task in the after analyses. In a second step, emotional and non-emotional judgment tasks were compared directly with each other as well as with baseline [Price and Friston, 1997]. This allowed for differentiation between relative signal changes (between conditions) and true signal changes (referring to baseline).

Due to our a priori hypothesis with focus on the prefrontal cortex, we set the level of significant regional activity changes to $Z > 3.03$ ($P < 0.001$ uncorrected, voxel level; $P < 0.05$ corrected, cluster level) thereby achieving a high level of sensitivity for detection of both signal increases and decreases [Editorial, 2001; Gusnard et al., 2001; Gusnard and Raichle, 2001; O'Doherty et al., 2001]. The anatomic localization of local maxima was assessed by reference to the MNI brain as provided by SPM. The stereotactic coordinates of the voxels of local maximum significant activation were determined within regions of significant activity change. Regions of interest were medial and lateral prefrontal cortical areas including ventromedial prefrontal cortex (VMPFC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC) and dorsolateral prefrontal cortex (DLPFC) as briefly described below [Rajkowska and Goldman-Rakic, 1995]. The VMPFC covers the ventral part of the superior and medial frontal gyrus including the frontal pole. The DMPFC covers the dorsal part of superior and medial frontal gyrus. The VLPFC covers the ventral parts of the inferior frontal gyrus. The DLPFC covers the middle (i.e., dorsal) part of the middle frontal gyrus. Because the entire medial and lateral prefrontal cortex was the focus of our study, we also included other dorsally located lateral prefrontal cortical areas (e.g., dorsal parts of the inferior frontal gyrus), as distinguished from the DLPFC, in our analysis. To account for this broader definition of the dorsal parts of the lateral prefrontal cortex, we called this area (d)LPFC.

RESULTS

There were no significant differences in reaction times between emotional (1,231.4 ± 170.8 msec) and non-emotional (1,280.4 ± 184.4 msec) judgment tasks. Similarly, we found no significant differences in reaction times for emotional judgments of emotional (1,217.5 ± 171.6 msec) and non-emotional (1,245.3 ± 193.3 msec) pictures or for the non-emotional judgments of emotional (1,307.4 ± 192.4 msec) and non-emotional 1,253.4 ± 182.8 msec) pictures.

FMRI results showed signal increases and decreases in medial and lateral prefrontal cortex in the comparison of judgment conditions (both emotional and non-emotional) with baseline (Table I, Fig. 2). Judgment tasks induced signal increases in VLPFC and (d)LPFC (Fig. 2A) and concurrent signal decreases in VMPFC and DMPFC (Fig. 2B). Although not the primary focus of the present study, further regions were found to be involved in judgment tasks. Comparison between judgment conditions and baseline showed signal increases in left parietal cortex ($-28/-52/50$; $Z = 3.93$), bilateral posterior insula ($-58/-2/-1$, $Z = 3.36$; $53/-15/-6$, $z = 3.41$) and premotor/motor cortex ($4/8/48$, $z = 3.58$).

The emotional judgment task showed relative signal increases in VMPFC and DMPFC when compared to the non-emotional judgment task (Figs. 3A and 4A). As shown in separate comparisons with baseline (Fig. 4B), these relative

Figure 2.

True signal changes (referring to baseline) in prefrontal cortical regions during judgment of IAPS pictures. (**A**) Signal increases in lateral prefrontal cortical regions during judgment of IAPS pictures as compared to baseline. (**B**) Signal decreases in medial prefrontal cortical regions during judgment of IAPS pictures as compared to baseline. Only regions with $Z > 3.40$ ($P < 0.001$ uncorrected, voxel level; $P < 0.05$ corrected, cluster level) are described. All images shown represent group average. VMPFC, 4/56/6, $Z = -4.43$; DMPFC, 20/38/42, $Z = -4.00$; Right VLPFC, 44/46/6, $Z = 4.06$ and 40/43/15, $Z = 3.21$; Left VLPFC, −34/52/6, $Z = 3.26$; Right (d)LPFC, 44/8/24, $Z = 4.90$. In fMRI images areas of significant signal changes are shown as through projections onto representations of standard stereotaxic space in sagittal, coronal and transverse projections. FMRI images represent results of group analyses depicted on a standard MNI brain. The sagittal view in fMRI images depicts the right hemisphere. Note the reciprocal modulation (i.e., signal increases and decreases) in medial and lateral prefrontal cortical regions during judgment tasks. VLPFC and (d)LPFC show signal increases, whereas VMPFC and DMPFC can be characterized by signal decreases.

Figure 3.

Comparison between emotional and non-emotional judgment. **A:** Emotional judgment versus non-emotional judgment: VMPFC and DMPFC. **B:** Non-emotional judgment versus emotional judgment: VLPFC and (d)LPFC. Only regions with $Z > 3.03$ ($P < 0.001$ uncorrected, voxel level; $P < 0.05$ corrected, cluster level) are described. All images shown represent group average. VMPFC, −4/54/16, $Z = 4.007$; DMPFC, −8/40/41, $Z = 3.37$; Right VLPFC, 44/46/6, $Z = 3.17$ and 45/51/3, $Z = 3.03$; Right (d)LPFC, 48/8/24, $Z = 3.13$; Left (d)LPFC, −50/6/34, $Z = 3.15$. In fMRI images areas of significant signal changes are shown as through projections onto representations of standard stereotaxic space in sagittal, coronal and transverse projections. FMRI images represent results of group analyses depicted on a standard MNI brain. The sagittal view depicts the right hemisphere. Note that direct comparison between emotional judgment and non-emotional judgment shows relative signal increases in medial prefrontal regions, whereas no signal changes are detected in lateral prefrontal cortex. In contrast, the comparison between non-emotional judgment and emotional judgment shows relative signal increases in lateral prefrontal regions, whereas no signal changes are detected in medial prefrontal cortex.

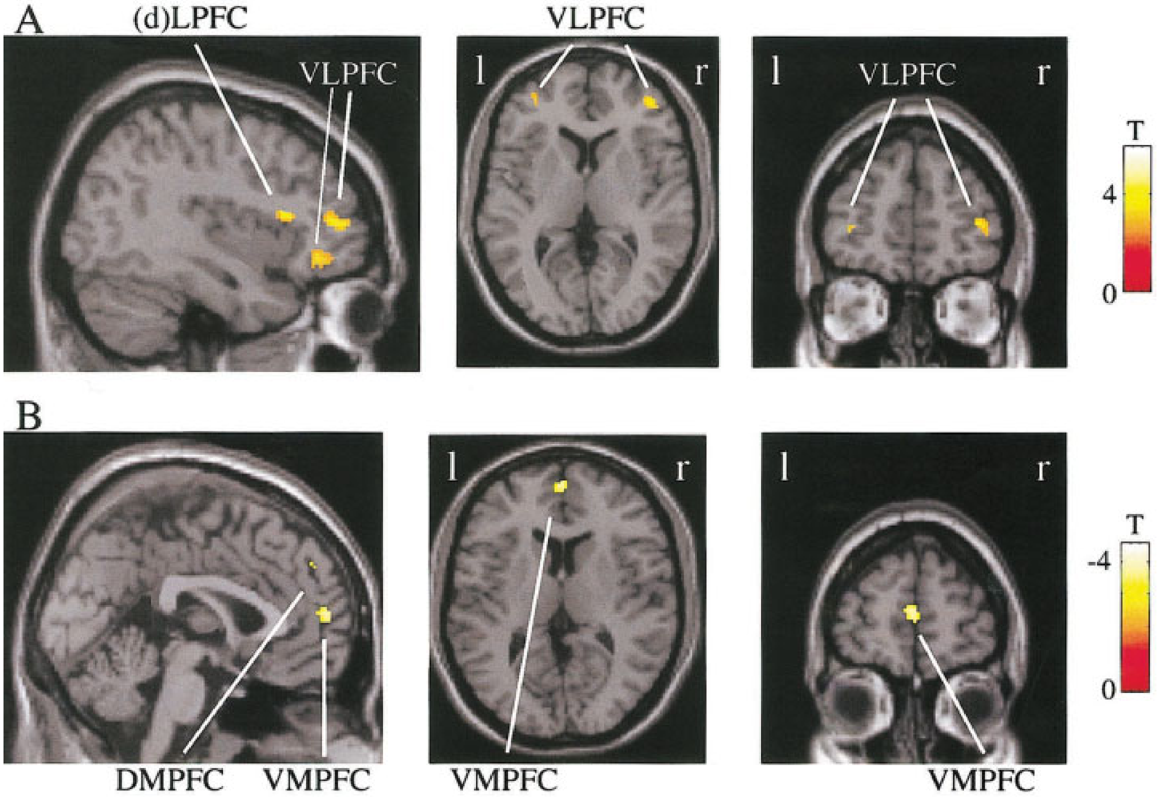

Figure 2.

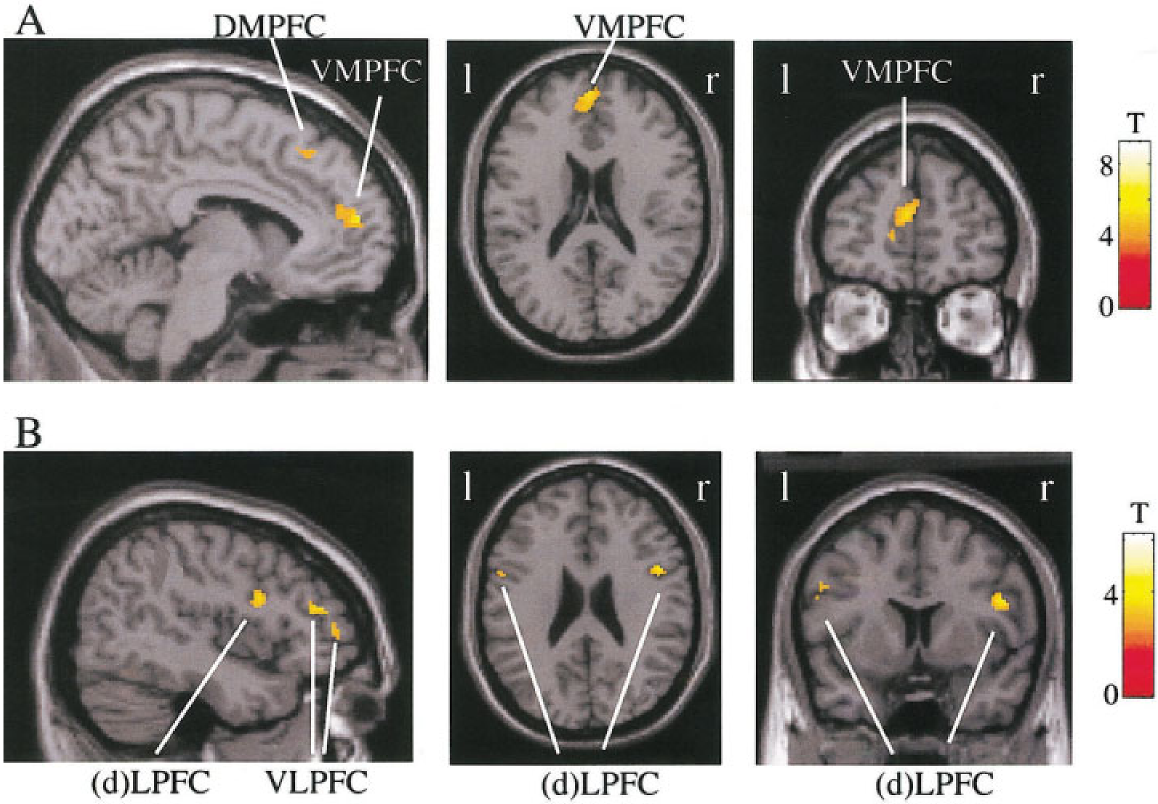

Figure 3.

TABLE II. Comparison between passive viewing and judgment

	Judgment > passive viewing		Passive viewing > judgment	
Brain region	x, y, z*	Z**	x, y, z*	Z**
VMPFC	—	—	0, 30, 6	3.62
DMPFC	—	—	10, 46, 38	3.56
rVLPFC	36, 32, 10	4.02	—	—
lVLPFC	−38, 34, 12	3.35	—	—
r(d)LPFC	42, 8, 20	3.52	—	—
l(d)LPFC	−40, −2, 26	4.12	—	—

* Montreal Neurological Institute coordinates given by x, y, z (in mm). Coordinates describe right(+)/left(−) (x), anterior(+)/posterior(−) (y), and superior(+)/inferior(−) distances (z).
** Z-score for maximally activated foci within the respective region. Only foci with $Z > 3.19$ ($P < 0.001$ uncorrected, voxel level) were considered.
VMPFC, ventromedial prefrontal cortex (PFC); DMPFC, dorsomedial PFC; rVLPFC, right ventrolateral PFC; lVLPFC, left ventrolateral PFC; r and l(d)LPFC, right and left dorsally located lateral PFC regions (including dorsolateral PFC and dorsal parts of the inferior frontal gyrus).

signal changes were due to smaller true signal decreases (below baseline) in VMPFC and DMPFC during emotional judgment compared to non-emotional judgment.

The non-emotional judgment task showed relative signal increases in VLPFC and (d)LPFC when compared to the emotional judgment task (Figs. 3B and 4A). As shown in separate comparisons with baseline (Fig. 4B), these relative signal increases were due to smaller true signal increases (above baseline) in emotional judgment compared to non-emotional judgment. Thus, the emotional load in the judgment task (i.e., *emotional* judgment) led to attenuation of both signal decreases in VMPFC/DMPFC and, at the same time, signal increases in VLPFC/(d)LPFC, resulting in a pattern of reciprocal attenuation. The comparison of signal changes between male and female subjects did not show significant differences.

To investigate valence effects separately, we tested for parametric (linear) relationship between the magnitudes of signal changes and the emotional valences of the presented pictures. Results showed valence-dependent modulation of signal changes in VMPFC during judgment tasks compared to baseline. The more negative the presented picture, the more negative the signal percent change in VMPFC. These results will be reported in detail in a separate article.

Though not the primary focus of the present study, further regions showed signal increases in the comparison between emotional judgment and non-emotional judgment. Emotional judgment induced true signal increases (above baseline) in supragenual anterior cingulate (2/24/18, $Z = 3.60$), bilateral anterior insula (−44/18/0, $Z = 4.16$; 54/8/−8, $Z = 3.83$), posterior cingulate (0/−10/36; $z = 4.23$) and left parietal cortex (−50/−58/14, $Z = 4.93$).

Passive viewing and judgment could not be compared because these conditions had not been properly separated by baseline. The onsets of passive viewing and judgment were only spaced by 2 sec so that the corresponding hemodynamic regressors were correlated (non-orthogonal). This precluded any statement about differences between passive viewing and judgment.

DISCUSSION

We investigated medial and lateral prefrontal cortical function during emotional–cognitive interaction using fMRI. Our main findings included: (1) both emotional and non-emotional judgment of IAPS pictures were characterized by signal increases in VLPFC/(d)LPFC and concurrent signal decreases in VMPFC/DMPFC; (2) direct comparison between emotional and non-emotional judgment showed relative signal increases in VMPFC/DMPFC; in contrast, relative signal increases were detected in VLPFC/(d)LPFC when comparing non-emotional to emotional judgment; and (3) as shown in separate comparisons with baseline, these relative signal changes were due to smaller signal decreases in VMPFC/DMPFC as well as smaller signal increases in VLPFC/(d)LPFC during emotional judgment.

The results confirm our hypothesis of reciprocal modulation and attenuation in medial and lateral prefrontal cortical regions during emotional–cognitive interaction. First, we observed reciprocal modulation between medial and lateral prefrontal cortical regions in our cognitive task (judgment). Second, inclusion of an emotional component into the cognitive (i.e., judgment) task lead to smaller signal decreases in VMPFC/DMPFC and, at the same time, smaller signal increases in VLPFC/(d)LPFC. This means that in the emotional condition the signals were closer to baseline and will be referred to as attenuation. Because attenuation concerned both medial and lateral prefrontal cortical regions in opposite directions (i.e., smaller signal decreases/increases respectively), we speak of reciprocal attenuation. Our findings are thus in accordance with the above postulated functional mechanisms of reciprocal modulation and attenuation of prefrontal cortical activity during emotional–cognitive interaction. Both functional mechanisms are schematically illustrated in Figure 5 and will be explained in further detail.

Reciprocal Modulation Between Medial and Lateral Prefrontal Cortex During Judgment of IAPS Pictures

In accordance with previous studies [Gorno-Tempini et al., 2001; Hariri et al., 2000; Lange et al., 2003; Nakamura et al., 1999], we observed signal increases in lateral prefrontal cortical regions (i.e., VLPFC and (d)LPFC) during both emotional and non-emotional judgment of IAPS pictures when compared to baseline. In addition, we detected simultaneous signal decreases in VMPFC and DMPFC during both emotional and non-emotional judgment tasks. Such signal decreases in medial prefrontal regions have also been reported for various cognitive tasks, including noun generation, object knowledge, impersonal/personal word judgment, as well as emotional and non-emotional judgment [Ferstl and von Cramon, 2002; Gusnard et al., 2001; Kelley et al., 2002; Mitchell et al., 2002; Simpson et al., 2000, 2001]. Our findings complement these observations by showing simultaneous occurrence of opposite signal changes (i.e., signal decreases and increases) in medial and lateral prefrontal cortex. One may speak consequently of reciprocal modulation in medial and lateral prefrontal cortex during cognitive processing as reflected in our emotional and non-emotional judgment tasks. A similar functional mechanism of reciprocal modulation though in a reverse way has been postulated in the case of mood induction and major depressive disorder [Drevets and Raichle, 1998; Liotti et al., 2002; Mayberg et al., 1999]. In this case the medial prefrontal cortex shows activation (i.e., signal increases), whereas the lateral prefrontal cortex shows deactivation (i.e., signal decreases; see Fig. 5A for illustration).

Analogous patterns of reciprocal modulation have been observed previously in other cortical regions such as ipsi- and contralateral motor cortex [Allison et al., 2000], subgenual anterior cingulate and right prefrontal cortex [Liotti et al., 2002; Mayberg et al., 1999], pregenual and supragenual anterior cingulate [Bush et al., 2000], medial and lateral orbitofrontal cortex [O'Doherty et al., 2001], visual and auditory cortex [Laurienti et al., 2002] and striate and extrastriate visual cortex [Kleinschmidt et al., 1998].

We did not obtain any significant differences in signal changes between female and male subjects. It should be considered, however, that the female:male ratio was rather unbalanced in the present study. Emotional imaging studies focusing on gender differences showed differences in signal changes rather in the amygdala than in prefrontal cortical regions [Canli et al., 2002; Lee et al., 2002; Schneider et al., 2000; Zald, 2003].

It should be noted that the exact physiological meaning of signal decreases in fMRI, as distinguished from signal increases, has not yet been elucidated [Gusnard and Raichle, 2001; Logothetis et al., 2001]. It remains unclear whether these signal decreases reflect neural inhibition or reduced excitatory input. The exact physiological interpretation of the observed signal decreases remains therefore uncertain.

Reciprocal Attenuation in Prefrontal Cortex During Emotional–Cognitive Interaction

Inclusion of the emotional component into the judgment task (emotional judgment) resulted in relative signal increases in ventro- and dorsomedial prefrontal cortex compared to the non-emotional judgment task. In contrast, the non-emotional judgment task was associated with relative

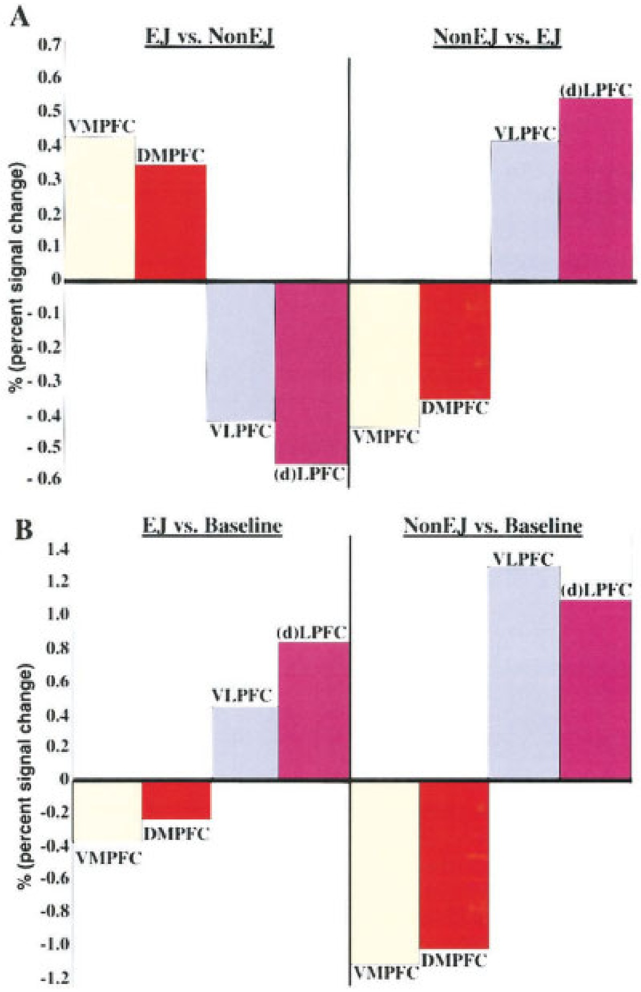

Figure 4.

Comparison between emotional judgment, non-emotional judgment, and baseline. **A:** Direct comparisons: emotional versus non-emotional judgment; non-emotional versus emotional judgment. **B:** Separate comparisons with baseline: emotional judgment versus baseline, non-emotional judgment versus baseline. EJ, emotional judgment; NonEJ, non-emotional judgment. Only activated foci with $Z > 3.32$ ($P < 0.001$ uncorrected, voxel level; $P < 0.05$ corrected, cluster level) are described. MNI coordinates and Z-scores are similar to those described in Figure 3. The depicted bar diagrams represent average values as calculated from the values of the single subjects. For each subject and contrast the maximum voxel value within the respective region (VLPFC, (d)LPFC, VMPFC, DMPFC) was used. Accordingly, the magnitudes displayed in (B) do not precisely sum to the magnitudes displayed in (A). Values from right and left side were averaged for VLPFC and (d)LPFC respectively. Note that direct comparisons between emotional and non-emotional judgment conditions showed relative signal changes, as demonstrated in separate comparisons with baseline. Relative signal increases in VMPFC/DMPFC in emotional judgment compared non-emotional judgment were due to smaller true signal decreases (below baseline) in emotional judgment. In contrast, relative signal increases in VLPFC/(d)LPFC in non-emotional judgment compared to emotional judgment were due to higher true signal increases (above baseline) in non-emotional judgment (note higher values in percent signal change in non-emotional judgment).

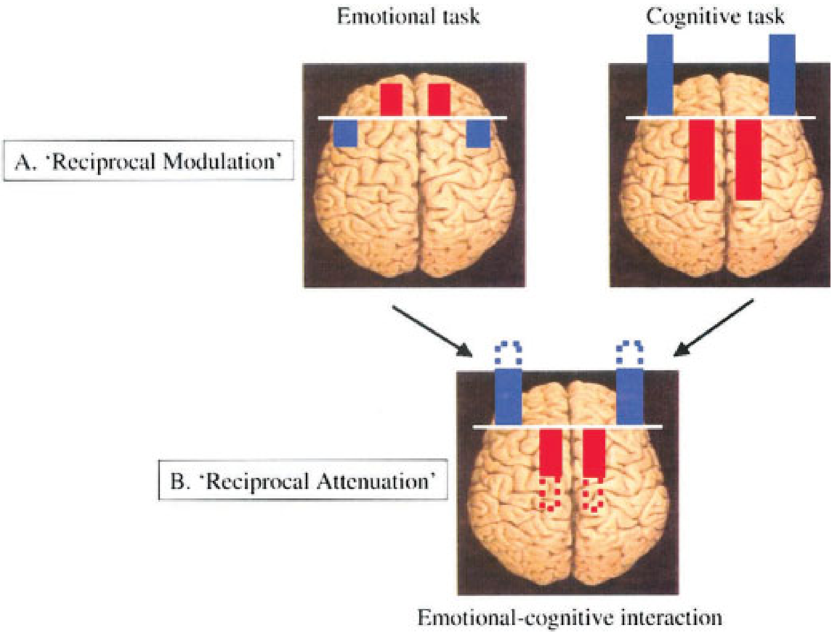

Figure 5.

Schematic presentation of reciprocal modulation and attenuation in medial and lateral prefrontal cortex. (**A**) Reciprocal modulation. It can be defined by signal changes in opposite directions in different regions. Whereas emotional processing leads to signal increases in medial prefrontal cortical regions and concurrent signal decreases in lateral prefrontal cortex, cognitive processing induces the reverse pattern with signal increases in lateral prefrontal cortex and signal decreases in medial prefrontal cortex. (**B**) Reciprocal attenuation. Inclusion of an emotional component into a cognitive task leads to smaller signal decreases in medial prefrontal cortical regions and smaller signal increases in lateral prefrontal cortical regions. In the emotional condition the signals are closer to baseline that is called attenuation. Because attenuation concerned both medial and lateral prefrontal cortical regions in opposite directions, we speak of reciprocal attenuation. This figure is not intended to depict specific values collected in our study, but does illustrate the functional mechanisms of reciprocal modulation and attenuation as derived from our results and previous studies. Blue bars represent activity changes in lateral, red bars in medial prefrontal cortical regions. Activations and deactivations are referred to baseline (white line). Hemispheric asymmetries related to certain aspects of emotional and cognitive processing are not taken into account here.

signal increases in lateral prefrontal cortical regions compared to the emotional judgment task. These findings are in accordance with previous studies on emotional–cognitive interaction. Using a verbal fluency task, Baker et al. [1997] observed lower regional cerebral blood flow (rCBF) in the DLPFC in the emotional conditions compared to the non-emotional condition. Simpson et al. [2000] showed larger BOLD signals in the DMPFC and subgenual anterior cingulate gyrus (among other regions) when negative emotional stimuli were used for the cognitive task compared to neutral stimuli. Gusnard et al. [2001] reported activity increases in the DMPFC in an emotional judgment task compared to a non-emotional judgment task.

Our results critically extend these findings in the following ways. First, we show that not only dorsally located regions in medial and lateral prefrontal cortex, but also ventral prefrontal regions (i.e., VLPFC and VMPFC) are involved in emotional–cognitive interaction. Second, our findings demonstrate that differences in signal response between emotionally loaded and non-emotional cognitive tasks are compatible with the functional mechanism of reciprocal attenuation. Relative signal increases in ventro- and dorsomedial prefrontal cortex in emotional compared to non-emotional judgment were shown to be due to smaller true signal decreases in the emotionally loaded condition. Similarly, relative signal increases in ventrally- and dorsally located lateral prefrontal cortical regions in non-emotional compared to emotional judgment were shown to be due to larger absolute signal increases in the non-emotional condition. This means that in the emotional condition the signals were closer to baseline that may be called attenuation. Because attenuation occurs in both medial and lateral prefrontal cortical regions in opposite directions (i.e., smaller signal decreases/increases respectively), we speak of reciprocal attenuation (Fig. 5B).

Randomization of single trials in an event-related design enabled inclusion of sustained baseline periods between single trials that in turn allowed for differentiation between relative signal changes (between conditions) and true signal changes (referring to baseline). As a result we were able to detect the pattern of reciprocal attenuation in medial and lateral prefrontal cortex. Without consideration of a baseline the distinction between relative and true signal decreases would have remained impossible.

Strictly speaking, so-called true signal changes as reported in our study must be regarded as relative to our resting baseline and it should be noted that inclusion of a different type of baseline might have led to different results [Newman et al., 2001; Stark and Squire, 2001]. One might distinguish between a resting baseline, intended to induce a resting state [Gusnard et al., 2001; Raichle et al., 2001], and a control baseline that serves as a control condition [O'Doherty et al., 2001].

In conclusion, our results are in accordance with the functional mechanism of reciprocal modulation and attenuation. Physiologically, this mechanism might allow for adjustment of concurrent neural processes. Psychologically, this might subserve emotional–cognitive interaction as reflected in our ability to weight, integrate and reciprocally adjust emotional and cognitive demands within a task [Bartolic et al., 1999]. Psychopathologically, disturbances of reciprocal modulation might account for co-occurrence of certain emotional and cognitive symptoms in psychiatric disorders such as major depression. Depressive patients show both increased neural activity in the VMPFC and decreased neural activity in the DLPFC as compared to healthy subjects [Brody, 2001; Drevets et al., 2001; Mayberg et al., 1999]. Thus, maladjustment of reciprocal modulation and attenuation might account for both emotional (e.g., sadness, anxiety) and cognitive (e.g., deficits in attentional set-shifting) [Austin et al., 1999; Murphy et al., 1999] deficits in depressive patients.

ACKNOWLEDGMENTS

The study was supported in part by the federal state of Sachsen-Anhalt (to A.H.), the National Institutes of Mental Health (RO1MH57980, RO1MH60734), the National Alliance for Research in Schizophrenia and Depression (NARSAD; to A.P.L.), a Clinical Scientist Development Award from the Doris Duke Foundation, and a Clinical Hypothesis Program in Imaging from the Dana Foundation (to G.S.), the post-doctorate program of the German Academic Exchange Service (DAAD; D/02/46858 to F.B.), and a Heisenberg grant from the German Research Foundation (DFG, 304/4-1 to G.N.).

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