GABA-ergic Modulation of Prefrontal Spatio-temporal Activation Pattern during Emotional Processing: A Combined fMRI/MEG Study with Placebo and Lorazepam

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Abstract

■ Various prefrontal cortical regions have been shown to be activated during emotional stimulation, whereas neurochemical mechanisms underlying emotional processing in the prefrontal cortex remain unclear. We therefore investigated the influence of the GABA-A potentiator lorazepam on prefrontal cortical emotional–motor spatio-temporal activation pattern in a combined functional magnetic resonance imaging/magnetoencephalography study. Lorazepam led to the reversal in orbito-frontal activation pattern, a shift of the early magnetic field dipole from the orbito-frontal to medial prefrontal cortex, and alterations in premotor/motor cortical function during negative and positive emotional stimulation. It is concluded that negative emotional processing in the orbito-frontal cortex may be modulated either directly or indirectly by GABA-A receptors. Such a modulation of orbito-frontal cortical emotional function by lorazepam has to be distinguished from its effects on cortical motor function as being independent from the kind of processing either emotional or nonemotional. ■

INTRODUCTION

Several imaging studies have demonstrated strong activation in the orbito-frontal, lateral prefrontal, and premotor cortex in healthy subjects during emotional processing (Northoff, Richter, et al., 2000; Büchel, Morris, Dolan, & Friston, 1998; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Baker, Frith, & Dolan, 1997; Imaizumi et al., 1997; Irwin et al., 1997; Lane, Reimann, Ahern, Schwartz, & Davidson, 1997; Lane, Reimann, Bradley, et al., 1997; Paradiso et al., 1997; Phillips et al., 1997; Morris et al., 1996, 1998; George et al., 1995; Pardo, Pardo, & Raichle, 1993). Most studies report activation of different cortical regions during negative and positive emotional processing (Northoff, Richter, et al., 2000; Baker et al., 1997; Imaizumi et al., 1997; Irwin et al., 1997; Lane, Reimann, Ahern, et al., 1997; Lane, Reimann, Bradley, et al., 1997; Morris et al., 1996, 1998; George et al., 1995) whereas only some authors postulate similar neuroanatomical substrates for processing of negative and positive emotions in the prefrontal cortex (Beauregard et al., 1998) and/or amygdala (Phelps, LaBar, Gatenby, O'Connor, & Gore, 1998; Breiter et al., 1996). Several authors found activation (i.e., positively correlated activity) in the orbito-frontal cortex during negative emotional stimulation as well as activation in the lateral prefrontal cortex in positive emotions (Northoff, Richter, et al., 2000; Mayberg et al., 1999; Morris et al., 1998; Baker et al., 1997; Irwin et al., 1997; Paradiso et al., 1997; Philipps et al., 1997; George et al., 1995; Pardo et al., 1993). In a study conducted by our own group (Northoff, Richter, et al., 2000) we found a high proportion of decreases in signal (i.e., negatively correlated activity) in the orbito-frontal cortex during positive emotions whereas in negative emotions signal decreases were most pronounced in the lateral prefrontal cortex. Depending on the interpretation of signals decreases (i.e., negatively correlated activity; see Methodological Limitations), these findings would be in accordance with PET studies reporting increases and decreases in activity in similar regions. Baker et al. (1997) found increased orbito-frontal and decreased lateral prefrontal cortical activity during negative emo-

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tional stimulation, which has been supported by other studies (Mayberg et al., 1999; Paradiso et al., 1997; George et al., 1995). In contrast, positive emotional stimulation led to decreased orbito-frontal (Paradiso et al., 1997) and increased lateral prefrontal (Baker et al., 1997) cortical activity.

Considering such patterns of concurrent increases and decreases in signals in the orbito-frontal and lateral prefrontal cortex, the question for the mechanisms of their apparently reciprocal functional regulation arises. Since emotional processing, especially negative emotional processing, seems to be closely related to GABA-A receptors in both animals (Corda et al., 1997; Crestani et al., 1999) and humans (Ferrara et al., 1999; Spanaki et al., 1999; Northoff, Krill, Eckert, Russ, & Pflug, 1998; Northoff, Steinke, Czerwenka, Danos, & Bogerts, 1999; Garcia et al., 1997), it may be hypothesized that such patterns of concurrent signal increases and decreases may be modulated (or even at least partially regulated) by substances, such as benzodiazepines, acting on GABA-A receptors (Raichle, 1998). There has been a study with midazolam, a benzodiazepine, showing dose-dependent decrease of regional cerebral blood flow (rCBF) in the orbito-frontal cortex (Veselis, Reinsel, & Feshchenko, 1998). However, modulation of regional prefrontal cortical function during emotional processing by benzodiazepines has never been demonstrated in humans. We therefore investigated the influence of a benzodiazepine, lorazepam, which shows a particularly strong anxiolytic effect (Northoff et al., 1999), on prefrontal cortical (see Figure 1) activity pattern during negative and positive emotional processing in a double-blind placebo-controlled study design.

RESULTS

Behavioral Data

Placebo

Reaction times are shown in Table 1. Variance analysis did not show any significant differences ($p = .735$) among the four conditions.

Preexperimental psychological states as measured with the Befindlichkeitsskala (BFs, see Methods) revealed a value of 13.33 ± 5.01 indicating no major stress in the actual psychological state. Ratings of valence, dominance, and arousal of pictures from International Affective Picture System (IAPS, see Methods) in healthy subjects did not differ from ratings in the already investigated healthy population (Lang, Bradley, & Cuthbert, 1997; Hamm & Vaitl, 1993).

Lorazepam

Reaction times are shown in Table 1. There were no significant differences ($p = .821$) among the four conditions within each group. However, analysis of variance (ANOVA) revealed a significant effect for group ($F = 4.2$, $p = .036$) with post hoc t tests showing significant differences between lorazepam and placebo subjects in negative ($p = .023$), positive ($p = .021$), and neutral ($p = .032$) conditions.

Preexperimental states as measured with the BFs before application of lorazepam showed no significant differences (14.56 ± 6.4) compared to subjects with placebo. Ratings of valence, dominance, and arousal of pictures from IAPS (see Methods) in healthy subjects with lorazepam did not differ from ratings in subjects with placebo.

Physiological and psychological measures of the efficacy of lorazepam/placebo can be seen in Figure 2. Only subjects with lorazepam showed alterations in all measures corresponding to findings by other authors (Hommer et al., 1986), whereas subjects receiving placebo showed no alterations at all.

In summary, subjects with lorazepam showed significantly longer reaction times in negative, positive, and neutral conditions than subjects receiving placebo.

Cortical Activation in Functional Magnetic Resonance Imaging (fMRI)

Placebo

Negative and positive emotional pictures led to different activation patterns in the orbito-frontal, lateral prefrontal, and premotor cortex. Negative emotional pictures induced strong signal increases in both magnitude and extent [i.e., positively correlated intensity weighted volume (IWVs) and voxels] in the medial orbito-frontal cortex and concomitant marked signal decreases (i.e., negatively correlated activity) in the lateral prefrontal cortex, whereas positive emotional processing could be characterized by an inverse pattern with strong signal increase in the lateral prefrontal cortex and marked signal decrease in the orbito-frontal cortex (see Table 2 and Figures 3 and 4 as well as Richter, 2001; Northoff, Richter, et al., 2000, for further details).

Lorazepam

Group × Region interaction as calculated by multivariate ANOVA (MANOVA) was (marginally) significant in the orbito-frontal ($F = 4.1, p = .021$), lateral prefrontal ($F = 2.3, p = .051$), and premotor ($F = 3.9, p = .013$) cortex.

Negative emotional processing. We found significantly ($F = 4.8–2.7$, $p = .0021–.0098$) lower positive IWV in the right and left orbito-frontal cortex in the negative–gray and negative–positive contrasts in lorazepam compared to placebo (see Table 2 and Figures 3 and 4). Furthermore, we found significantly ($F = 3.9–3.1$, $p = .0036–.0089$) decreased negative IWVs in the anterior cingulate, right and left lateral prefrontal, pre-

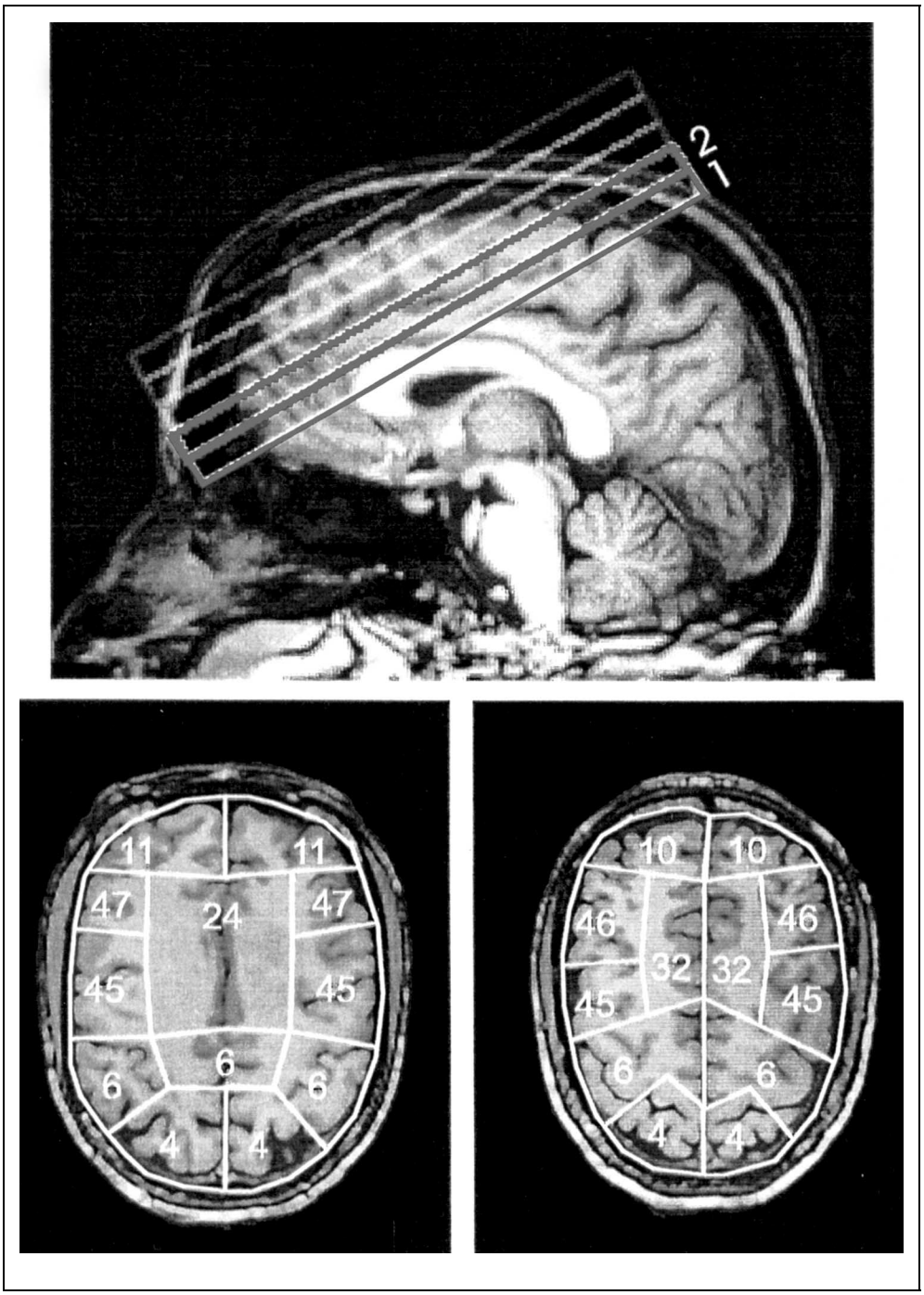

Figure 1. Placement of slices and determination of regions of interest (ROIs). Midsagittal view of slice placement (T1-weighted spin-echo sequences). Five images of contiguous oblique–axial planes with slice thickness of 8 mm and 64 × 64 voxels in plane were obtained from the whole frontal lobe. Slice angles were approximately 40° relative to the AC–PC line. In each slice, different anatomical ROIs were outlined anatomically without functional overlays. Regions were defined by landmarks according to Talairach coordinates (Talairach & Tounoux, 1988) covering the orbito-frontal, lateral prefrontal, medial prefrontal, cingular, premotor, and motor areas. Numbers within the different regions show the respective Brodmann's area. The two lowermost slices, as indicated with an arrow in A, are shown with their respective ROIs.

motor, and motor cortex in the negative contrasts (see Table 2). IWVs and voxels showed similar alterations in lorazepam (see Table 2 and Richter, 2001, the latter showing details of results for voxels).

In summary, we found significantly decreased positively correlated activity in the orbito-frontal cortex as well as significantly decreased negatively correlated activity in the lateral and premotor cortex in lorazepam.

Table 1. Reaction Times (msec) in Subjects With Placebo (n = 8) and Lorazepam (n = 8)

Subjects/Condition	*Negative*	*Positive*	*Neutral*	*Gray*
Placebo	516.84 ± 161.29	521.38 ± 177.89	533.61 ± 186.30	452.09 ± 140.36
Lorazepam	848.35 ± 287.11*	785.12 ± 240.18*	769.98 ± 206.61*	593.23 ± 127.44

*Significant difference ($p < .05$, corrected) between placebo and lorazepam.

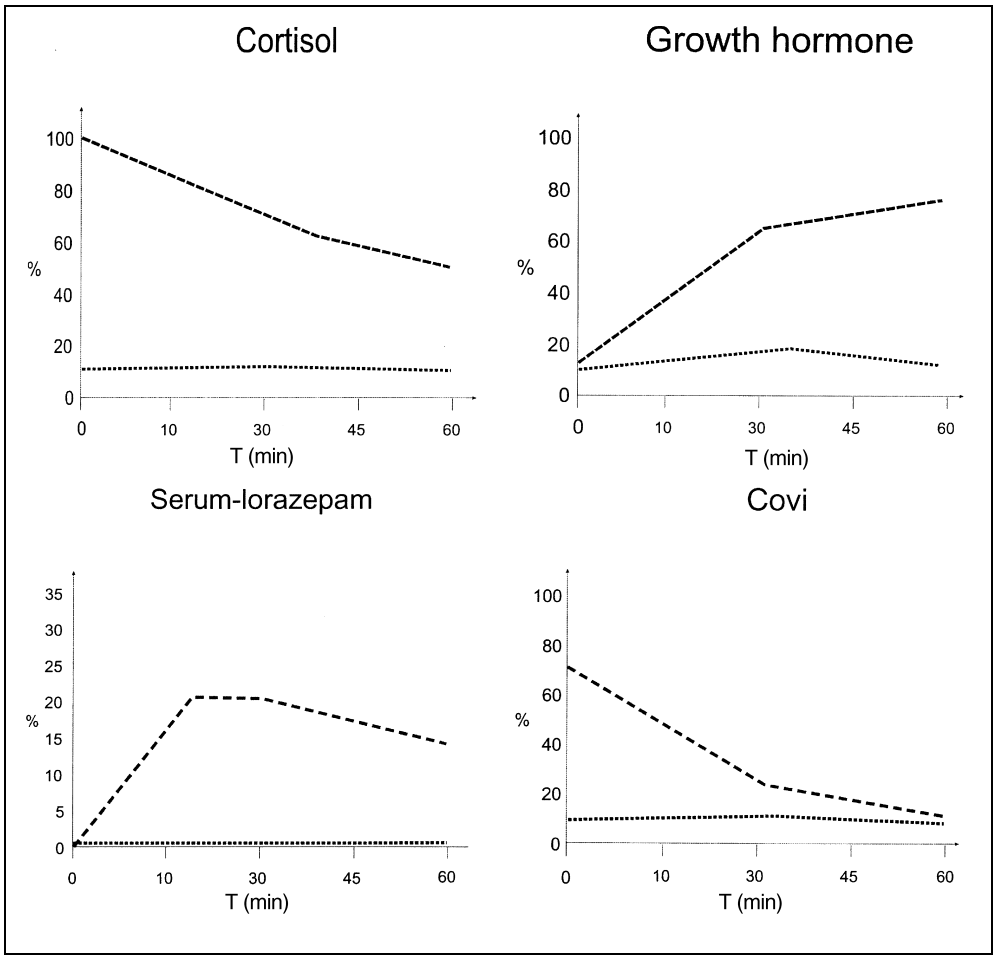

Figure 2. Neurochemical and psychological effects of lorazepam. *T*(min) = Time after intravenous administration of lorazepam/placebo; % = integral of percentage of change of the respective score/level obtained before lorazepam/placebo administration; Covi = Covi Anxiety Scale; Dotted line = subjects receiving placebo; Dashed line = subjects receiving lorazepam. Note the alterations in all four measures in subjects receiving lorazepam whereas those with placebo showed no alterations at all.

Positive emotional processing. We found significantly (F = 4.1–2.9, p = .0037–.0094) increased positive IWVs as well as significantly (F = 3.8–2.6, p = .0054–.0091) decreased negative IWVs in the right and left orbito-frontal cortex (see Table 2 and Figures 3 and 4). In addition, we found significantly (F = 3.9–2.8, p = .0048–.0089) lower positive IWV in the right and left lateral prefrontal and premotor cortex (see Table 2). IWVs and voxels showed similar alterations in lorazepam (see Table 2 and Richter, 2001, the latter showing details of results for voxels).

In summary, we found increased activation and decreased deactivation in the orbito-frontal cortex in subjects with lorazepam, which, in addition, could be characterized by decreased activity, namely, positive IWV in the lateral and premotor cortex.

Overall summary. First, orbito-frontal cortical function could be characterized by an opposite influence of lorazepam in negative and positive emotions with an increase of activation (positive IWV) in the latter and a decrease in the former (see Table 2 and Figure 4).

Second, orbito-frontal cortical function showed an almost inverse pattern of activation (positive IWV) and deactivation (negative IWV) before and after lorazepam in negative and positive emotions (see Table 2 and Figure 4).

Third, lorazepam showed a differential effect on lateral prefrontal cortical function in negative and positive emotions with regard to activation (modulation of positive IWV in positive emotions) and deactivation (modulation in negative emotions) (see Table 2).

Fourth, lorazepam lead to decreased activation (in positive emotions) and deactivation (in negative emotions) in the premotor/motor cortex.

Fifth, lorazepam showed no effect on orbito-frontal cortical activation (and premotor/motor cortex) with respect to attention/arousal (see neutral–gray contrast in Table 2) whereas such effects were clearly visible in the anterior cingulate and the medial and lateral prefrontal cortex.

Electromagnetic Signals in Magnetoencephalography (MEG)

Placebo

MEG signal analysis revealed movement-related magnetic fields with a motor field (MF) and movement-evoked fields (MEFI and II) whose underlying dipole could be anatomically localized in the anterior and posterior parts of primary motor cortex (see Table 3). In addition, an early magnetic field (EMF) in early time windows (−1700 to 1100 msec) was observed only in

Table 2. Group Means of Activity in the Prefrontal Cortical Regions during Negative and Positive Emotions in fMRI in Subjects with Placebo and Lorazepam

		Orbito-Frontal (BA 11,12)		*Anterior Cingulate (BA 24,2)*	*Medial Prefrontal (BA 8,9,10)*		*Lateral Prefrontal (BA 9,45,46,47)*		*Premotor (BA 6)*		*Motor (BA 4)*	
	Group	*Right*	*Left*		*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*
Negative emotions												
Neg–Neut	Placebo	87/−110	74/−173	46/−172	52/−93	55/−133	141/−205	155/−359	61/−68	59/−66	25/−37	29/−47
	Lorazepam	81/−86	65/−112	42/−125	61/−68	74/−40	90/−190	151/−150*	57/−21*	60/−35	54/−39	64/−28
Neg–gray	Placebo	288/−248	239/−314	136/−249	141/−168	190/−183	317/−681	336/−778	100/−298	147/−325	130/−136	148/−155
	Lorazepam	133*/202	119*/−209	87/−114*	121/−125	144/−51	265/−224*	343/−226*	156/−64*	168/−47*	136/−54*	130/−53*
Positive emotions												
Pos–Neut	Placebo	67/−153	63/−147	74/−60	118/−66	104/−68	314/−213	518/−260	256/−33	332/−46	100/−43	108/−54
	Lorazepam	168*/−132	245*/−113*	163*/−164*	114/−128	177/−110	208*/−236	465/−353	59*/−59	87*/−68	50/−24	91/−47
Pos–gray	Placebo	123/−224	109/−158	95/−49	161/−99	165/−87	508/−267	679/−231	339/−48	434/−57	122/−90	123/−81
	Lorazepam	211*/−104*	181*/−159	152*/−46	187/−82	161/−51	345*/−85*	483*/−130	140*/−19	123*/−23	124/−11	122/−50
Neg–Pos	Placebo	175/−107	131/−146	52/−88	90/−115	70/−155	139/−312	150/−500	29/−196	41/−243	55/−73	35/−85
	Lorazepam	66*/−103	44*/−151	56/−144	36/−106	35/−55	50/−158*	132/−210*	11/−26*	23/−27*	19/−44	36/−25
Neut–gray	Placebo	84/−62	72/−48	40/−38	86/−49	93/−33	134/−162	199/−193	51/−42	104/−80	15/−29	17/−61
	Lorazepam	92/−57	82/−56	171*/−57	183/−74	165/−55	421*/−115	459*/−167	75/−34	89/−47	70/−35	35/−85

+ = positively correlated IWVs; − = negatively correlated IWVs; IWV = intensity weighted volume (product of percentage of activation signal and volume, μl); BA = Brodmann's area; Neg = negative emotional pictures; Pos = positive emotional pictures; Neut = neutral pictures; Gray = gray pictures.

*Significant difference ($p < .01$) between placebo and lorazepam.

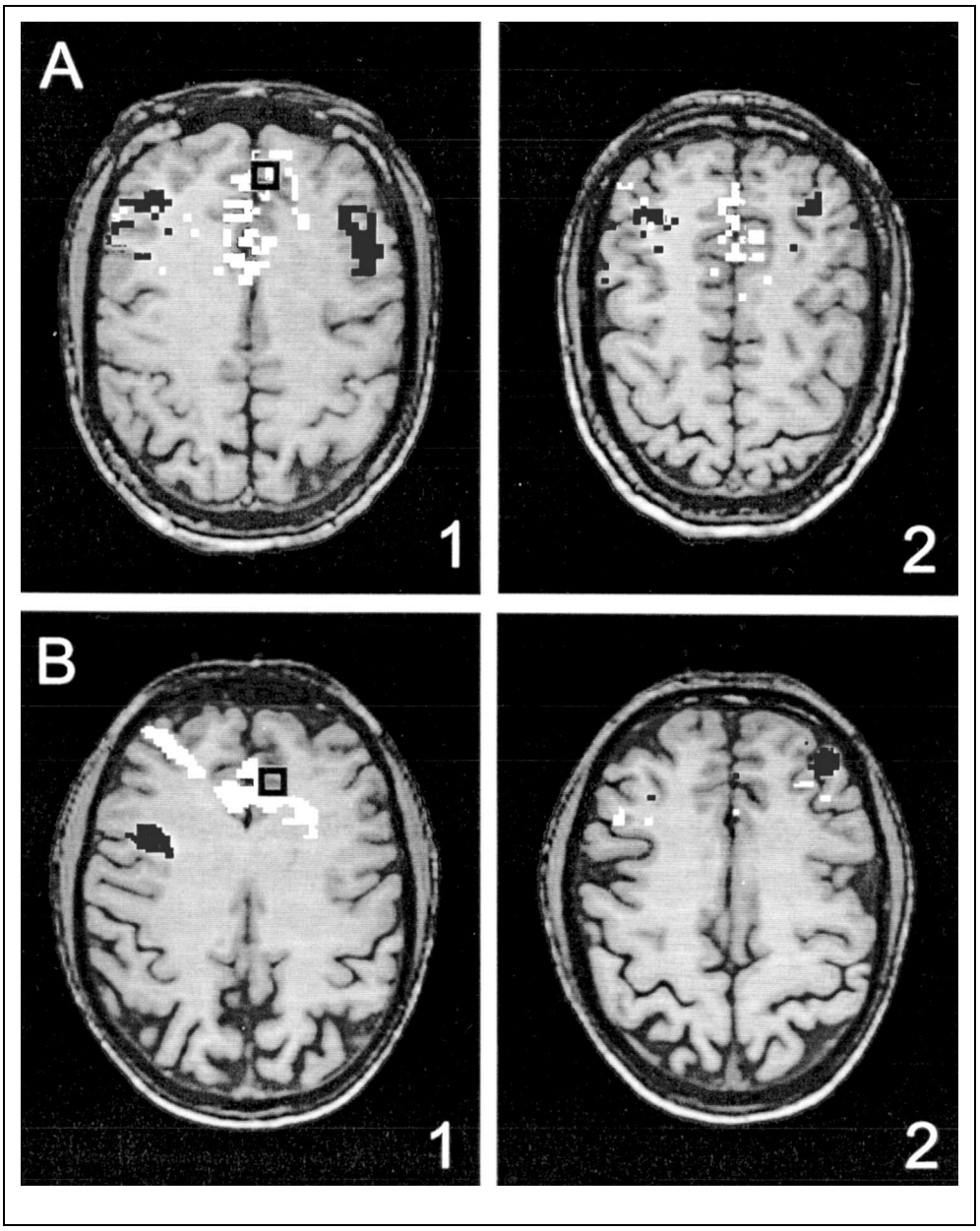

Figure 3. Localization of fMRI activity and the dipole of the EMF from MEG each matched into the same individual anatomical MRI image in a subject with lorazepam. (A) Activated areas and dipole of EMF in negative emotions in a subject with placebo. (B) Activated areas and dipole of EMF in negative emotions in a subject with lorazepam. (1) Lowermost slice (see also Figure 1). (2) Second lowermost slice (see also Figure 1). White pixels = positively-correlated voxels; Black pixels = negatively-correlated voxels; Squares = dipole of the EMF. The fMRI activity and the EMF 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 the subject with placebo (A) and by 7.9 mm in the subject with lorazepam (B). Note the shift of localization of fMRI signals and dipoles from EMF in the subject with lorazepam.

positive and negative emotional processing (see Table 4 and Figures 5 and 6) but not in either of the control conditions (neutral, gray). EMF showed an earlier onset, a higher strength, and a more medially oriented orbito-frontal location of underlying dipole in negative pictures than in positive pictures where a later onset, lower strength, and a more laterally orbito-frontal/prefrontal cortical anatomical localization of the underlying dipole was observed (see Northoff, Richter, et al., 2000, for further details).

Lorazepam

Movement-related magnetic field. Subjects with lorazepam showed significantly lower strength (RMS, dipole RMS) in MF and MEFI and II in all four conditions independent of emotional or non-emotional stimulation (see Table 3). Dipole RMS in the MF were significantly lower in negative ($F = 2.8$, $p = .023$) and positive ($F = 3.2$, $p = .031$) pictures as well as in motor-evoked fields (MEF) in positive ($F = 2.9$, $p = .034$) pictures (see Table 3).

EMF. No differences in strength of EMFs were found between the placebo and the lorazepam group (see Table 4).

Dipole source analysis. Dipoles for MF and MEFI showed quite low goodness-of-fit (GOF) so that, unlike in subjects receiving placebo, no satisfactory dipoles could be obtained in subjects with lorazepam. The dipole underlying the EMF in the negative and positive pictures was no longer located in the orbito-

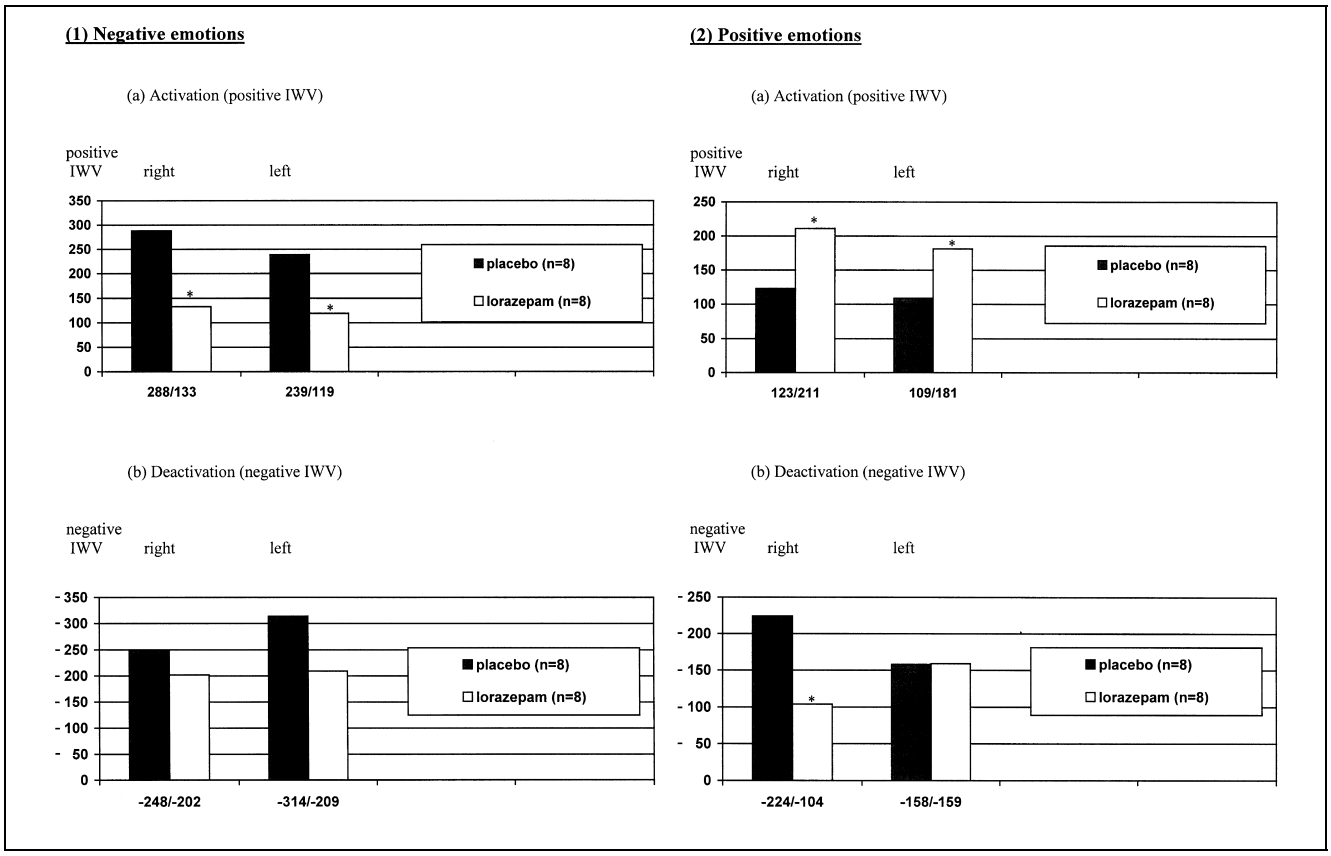

Figure 4. Means and *SD* of activity in the orbito-frontal cortex during negative and positive emotions in subjects with placebo and lorazepam in fMRI. (1) Negative emotions; (2) Positive emotions. (a) Activation (positive IWV). (b) Deactivation (negative IWV). *Significant difference ($p < .05$, corrected, Mann–Whitney *U* tests) between subjects with placebo and lorazepam. IWV = Intensity weighted volumes (product of the absolute number of voxels and average signal change in each ROI in all slices; Positive IWV = positively-correlated activity, i.e., IWV (positive numbers, probably reflecting activation); Negative IWV = negatively-correlated activity, i.e., IWV (negative numbers, probably reflecting deactivation). Note first the opposite influence of lorazepam on activation (positive IWV) in the orbito-frontal cortex in negative and positive emotions and, second, an almost reversed pattern of orbito-frontal cortical activation and deactivation in negative and positive emotions in subjects with placebo and lorazepam.

frontal cortex as in subjects with placebo but rather more superior and posterior in the medial prefrontal cortex (BA 8,10) in subjects receiving lorazepam (see Table 4 and Figures 3, 6, and 7). We found statistically significant differences ($F = 9.3–2.8$, $p = .000012–.032$) between placebo and lorazepam in negative emotions in all three coordinates (x, y, z) at −1600 and −1200 msec (see Table 4 and Figure 7). In positive emotions, dipole location differed significantly ($F = 7.5–3.2$, $p = .000023–.010$) in x and Z coordinates between placebo and lorazepam at −1600 and −1200 msec (see Table 4 and Figure 7). In addition, we found significant ($F = 6.8–3.4$, $p = .00045–.036$) differences in dipole location (x, y) between negative and positive emotions in placebo that were not found in subjects receiving lorazepam (see Table 4 and Figure 7).

In summary, subjects receiving lorazepam were characterized by a significantly different dipole localization of EMFs in the medial prefrontal cortex (and no longer in the orbito-frontal cortex as in subjects with placebo) as well as by significantly reduced strength in movement-related magnetic fields.

Correlations Between MRI/MEG Signals and Behavioral Measures

Placebo

Significant correlations were found only in negative emotional processing but not in contrasts involving positive emotional pictures. In the negative–gray contrast, significant positive correlations among reaction time and right medial prefrontal ($r = .714/p = .049$) and right motor ($r = .679/p = .044$) cortical signal increases were obtained (i.e., the longer the reaction time, the more signal increases). In addition, reaction time in negative emotional processing correlated significantly ($r = .934/.879$, $p = .021/.031$) with magnetic field strength (RMS/dipole RMS) in EMF (the longer the reaction time, the higher magnetic field strength) whereas such significant correlations were not found in any other condition (positive, neutral, gray).

Table 3. Comparison of Average Values for Movement-Related Magnetic Fields between Subjects Receiving Placebo (n = 8) and Those with Lorazepam (n = 8)

Condition	*Group*	*RMS (fT) (means ± SD)*	*Dipole RMS (fT) (means ± SD)*	*Q (nA) (means ± SD)*	*GOF (means ± SD)*	*Talairach Coordinates of Dipole*			*Anatomical Location*
						x	*y*	*z*	
MF (−51–50 msec)									
Negative	Placebo	59.69 ± 7.6	73.32 ± 14.2	59.17 ± 21.0	.91 ± 0.02	−26 ± 3	−18 ± 4	54 ± 2	left anterior motor (BA 4)
	Lorazepam	31.34 ± 8.5	37.88 ± 6.3*	36.27 ± 17.1	.57 ± 0.03	–	–	–	–
Positive	Placebo	65.84 ± 9.6	80.38 ± 17.4	58.20 ± 28.4	.88 ± 0.04	−25 ± 2	−17 ± 2	53 ± 3	left anterior motor (BA 4)
	Lorazepam	56.26 ± 9.7	63.04 ± 19.8*	99.35 ± 29.8	.49 ± 0.04	–	–	–	–
Neutral	Placebo	60.48 ± 11.4	87.45 ± 12.7	62.45 ± 18.5	.90 ± 0.03	−26 ± 2	−18 ± 3	54 ± 4	left anterior motor (BA 4)
	Lorazepam	47.37 ± 12.8	60.03 ± 18.4*	61.86 ± 19.2	.59 ± 0.02	–	–	–	–
MEFI (80–150 msec)									
Negative	Placebo	43.01 ± 8.9	57.61 ± 18.4	42.17 ± 23.5	.86 ± 0.03	−34 ± 4	−24 ± 3	57 ± 2	left posterior motor (BA 4)
	Lorazepam	34.67 ± 10.8*	49.72 ± 19.6	39.75 ± 20.8	.52 ± 0.04	–	–	–	–
Positive	Placebo	47.77 ± 8.4	55.11 ± 15.7	39.80 ± 13.5	.85 ± 0.05	−33 ± 1	−25 ± 2	58 ± 2	left posterior motor (BA 4)
	Lorazepam	40.23 ± 9.8	40.41 ± 16.6*	41.66 ± 14.7	.53 ± 0.03	–	–	–	–
Neutral	Placebo	45.30 ± 12.5	42.54 ± 8.7	26.17 ± 16.1	.87 ± 0.04	−34 ± 2	−24 ± 4	57 ± 3	left posterior motor (BA 4)
	Lorazepam	35.98 ± 14.8*	40.51 ± 9.2	32.53 ± 18.2	.59 ± 0.02	–	–	–	–

RMS = Root means square; fT = femtotesla; GOF = goodness of fit; BA = Brodmann's area; Q = strength in nanoampere (nA).

*Significant difference ($p < 0.01$, corrected) between placebo and lorazepam.

Table 4. Comparison of Average Values for EMFs between Subjects Receiving Placebo (n = 8) and Those with Lorazepam (n = 8)

Magnetic Field	*Time*	*Condition*	*Group*	*RMS (fT) (means ± SD)*	*Dipole RMS (fT) (means ± SD)*	*Q (nA)* (means ± *SD*)	*GOF > .85 (means ± SD)*	*Talairach coordinates of dipole*			*Anatomical Localization of Nearest Local Maximum in fMRI (BA)*	*Distances (mm) Between Dipole and fMRI*
								x	*y*	*z*		
EMF	−1,600 msec	Negative	Placebo	34.86 ± 6.8	47.74 ± 14.7	46.98 ± 18.5	.92 ± 0.06	1.3 ± 0.3[a,*]	43 ± 3[a,*]	−22 ± 2	medial orbito-frontal (BA 11)	8.7 ± 2.3
			Lorazepam	34.92 ± 7.9	47.69 ± 18.9	52.64 ± 20.2	.88 ± 0.04	1.7 ± 0.4[b,*]	33 ± 4[b,*]	−12 ± 3[b,*]	medial prefrontal (BA 9,10)	9.6 ± 3.6
		Positive	Placebo	24.00 ± 5.0	37.32 ± 14.8	23.89 ± 14.7	.90 ± 0.05	25 ± 4	35 ± 2	−21 ± 5	medio-lateral orbito/prefrontal (BA 11,47)	9.8 ± 4.5
			Lorazepam	27.08 ± 8.5	30.97 ± 12.0	42.84 ± 15.8	.86 ± 0.04	1.8 ± 0.4[b,*]	36 ± 4	−11 ± 3[b,*]	medial prefrontal (BA 10)	9.1 ± 4.8
		Neutral	Placebo	9.78 ± 3.9	–	–	–	–	–	–	–	
			Lorazepam	10.90 ± 3.1	–	–	–	–	–	–	–	
	−1,200 msec	Negative	Placebo	36.00 ± 9.8	49.01 ± 20.7	54.29 ± 19.0	.89 ± 0.05	1.8 ± 0.4[a,*]	44 ± 4[a,*]	−23 ± 3	medial orbito-frontal (BA 11)	7.5 ± 1.9
			Lorazepam	29.33 ± 6.8	44.06 ± 21.9	48.27 ± 21.7	.88 ± 0.04	5.5 ± 1.3[b,*]	33 ± 4[b,*]	−11 ± 3[b,*]	medial prefrontal (BA 9,10)	10.2 ± 3
		Positive	Placebo	32.22 ± 7.1	40.34 ± 13.7	39.47 ± 15.9	.90 ± 0.04	26 ± 5	35 ± 3	−21 ± 5	medio-lateral orbito/prefrontal (BA 11,47)	10.2 ± 3.2
			Lorazepam	30.69 ± 8.9	42.16 ± 14.9	40.87 ± 16.1	.85 ± 0.04	5.4 ± 1.2[b,*]	32 ± 4	−12 ± 3[b,*]	medial prefrontal (BA 9,10)	10.1 ± 3.4
		Neutral	Placebo	9.87 ± 5.1	–	–	–	–	–	–	–	–
			Lorazepam	12.56 ± 6.9	–	–	–	–	–	–	–	–

RMS = Root means square; fT = femtotesla; GOF = goodness of fit; BA = Brodmann's area.

[a]Negative placebo vs. positive placebo.

[b]Placebo vs. lorazepam.

*Significant difference (p < .01, corrected) between placebo and lorazepam.

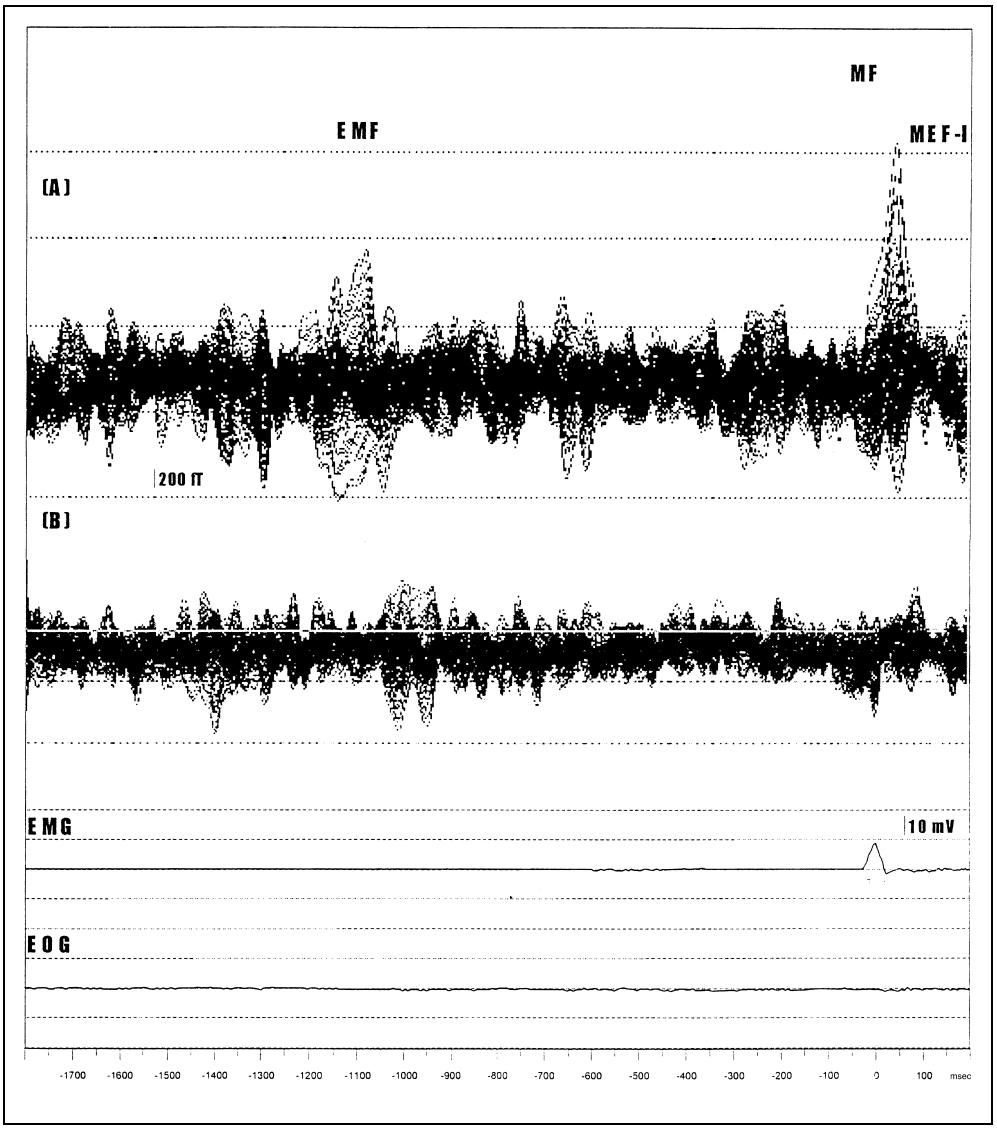

Figure 5. EMFs and movement-related magnetic fields in negative emotions in a subject with placebo and a subject with lorazepam. (A) Magnetic fields during negative emotions in a subject with placebo; (B) magnetic fields during negative emotions in a subject with lorazepam; EMF = early magnetic field; MF = motor field; MEF = 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 EMF in negative emotions in the subject with placebo and the alterations in movement-related magnetic fields in the subject with lorazepam.

In summary, subjects receiving placebo showed significantly positive correlations of reaction time with signal increases in right medial prefrontal/motor cortex and EMF strength only in negative emotional processing but not in any other condition.

Lorazepam

Reaction time correlated significantly negative with signals in the lateral prefrontal cortex in gray–neutral (signal decrease in right hemisphere: $r = -.821$, $p = .023$), gray–positive (signal decrease in right hemisphere: $r = -.786$, $p = .036$), and gray–negative (signal increase in left hemisphere: $r = -.786$, $p = .036$) contrasts (i.e., the longer reaction time, the less signals (increases or decreases) in the lateral prefrontal cortex). In addition, reaction time correlated significantly negative with signal decreases in right orbito-frontal cortex (neutral–negative: $r = -.857$, $p = .014$) and left motor cortex (positive–negative: $r = -.793$, $p = .033$) (i.e., the longer reaction time, the less signal decreases). Reaction times correlated significantly negative with strength (RMS/dipole RMS) of MF and MEF in positive ($r = -.876$–$.912$, $p = .034$–$.049$), negative ($r = -.821$–$.895$, $p = .033$–$.045$), and neutral ($r = -.899$–$.902$, $p = .021$–$.032$) conditions (i.e., the longer reaction time, the lower magnetic field strength).

In summary, subjects receiving lorazepam showed significantly negative correlations of reaction time with signal decreases in the orbito-frontal, lateral prefrontal, orbito-frontal, and motor cortex as well as with strength of movement-related magnetic fields.

DISCUSSION

We investigated the influence of lorazepam in a double-blind study design on prefrontal cortical spatio-temporal activation pattern during negative and positive emotional processing combining fMRI and MEG. We obtained the following main findings: (1) Reversal of

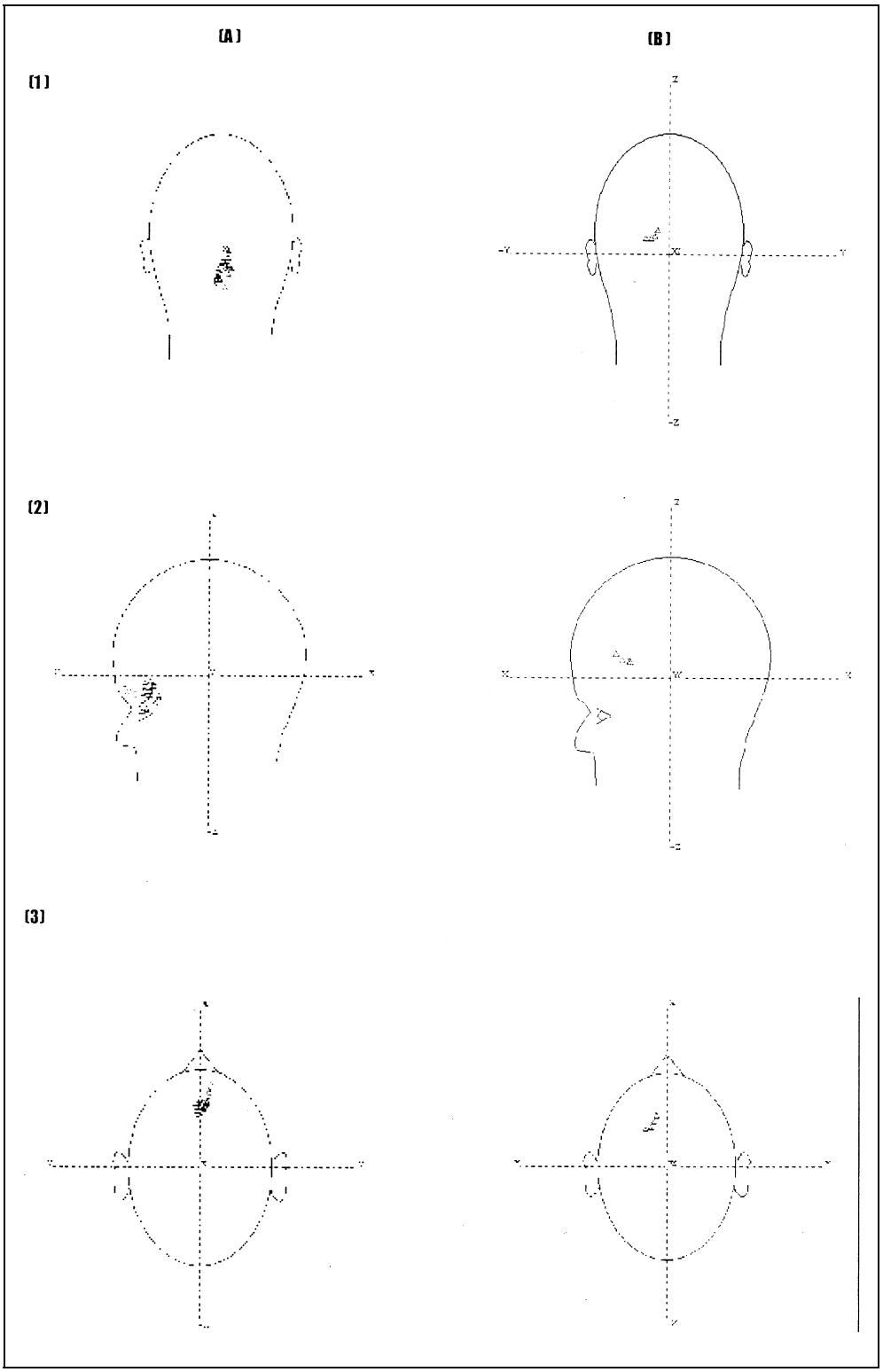

Figure 6. Location of the fittest dipoles for the EMF in a head coordinate system in negative emotions in a subject with placebo and a subject with lorazepam. (A) Dipoles in negative emotions in a subject with placebo. (B) Dipoles in negative emotions in a subject with lorazepam. (1) Head viewed from behind (*z*–*y* projection). (2) Head viewed from the right side (*x*–*z* projection). (3) Head viewed from above (*x*–*y* projection). Triangle = Dipoles of the EMF (−1700–1100 msec). Neuromagnetic fields were recorded from the whole scalp by use of a 148-channel BTI system. The locations are shown as projections in a head coordinate system. Scale is 2 cm. The fittest dipoles in EMFs were selected for each 50-msec epoch within the time windows given above. Note the shift of dipoles from orbito-frontal to medical prefrontal cortical areas in the subject with lorazepam.

orbito-frontal cortical activity (i.e., signal increases) in fMRI with low activity in negative pictures and high activity in positive pictures by lorazepam; (2) induction of a shift in location of dipole underlying the emotionally related EMF from orbito-frontal to medial prefrontal cortex in positive and negative emotional processing by lorazepam; (3) alteration in cortical motor function as reflected in lower premotor/motor cortical signals and reduced strength in movement-related magnetic field in subjects receiving lorazepam.

Results in the present study confirm our initial hypothesis of a relationship between orbito-frontal cortical activity and GABA-ergic neurotransmission during negative and positive emotional processing. The exact kind

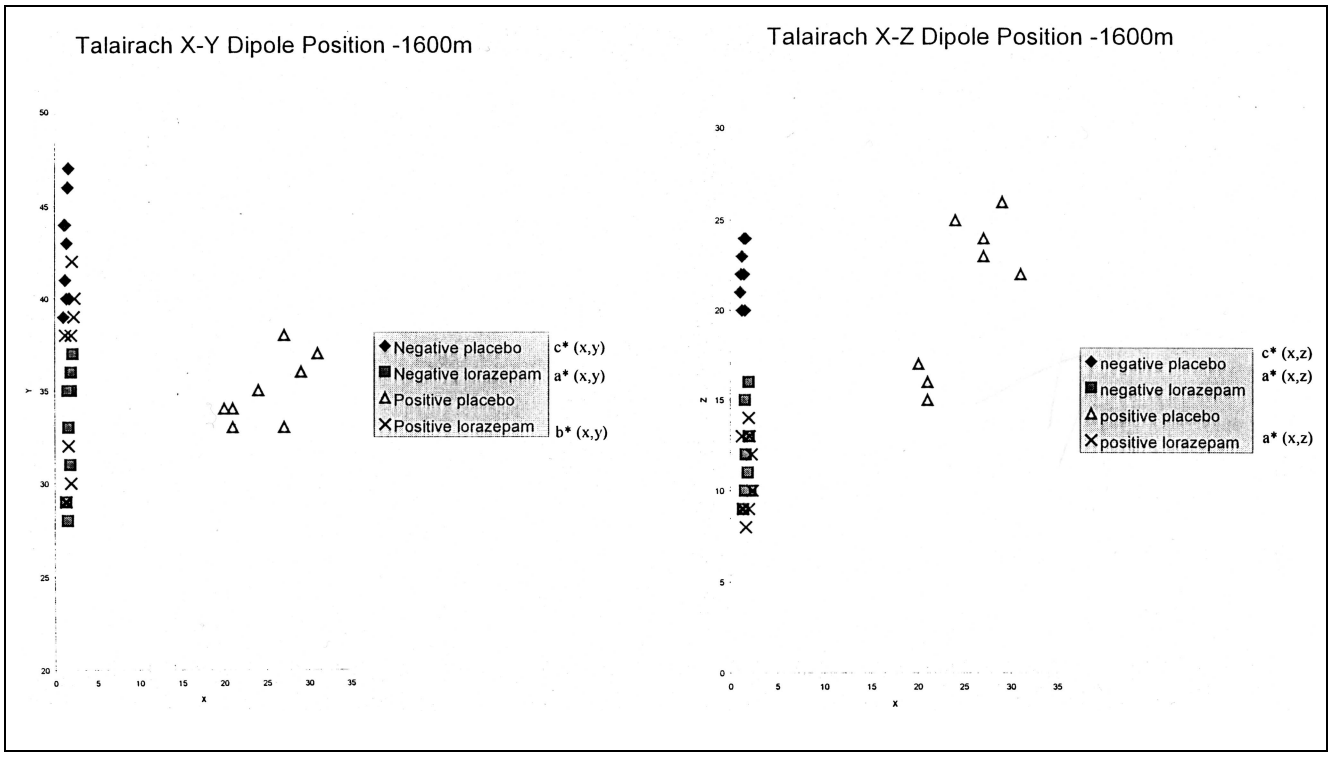

Figure 7. Plot of Talairach coordinates (*x*,*y*) (*x*,*z*) in negative and positive emotions for individual subjects with placebo ($n = 8$) and lorazepam ($n = 8$) in MEG. (1) *x*–*y* Talairach coordinates. (2) *x*–*z* Talairach coordinates.

[a]Significant difference in Talairach coordinates between placebo and lorazepam in negative emotions.
[b]Significant difference in Talairach coordinates between placebo and lorazepam in positive emotions.
[c]Significant difference in Talairach coordinates between negative and positive emotions in subjects with placebo.
[d]Significant difference in Talairach coordinates between negative and positive emotions in subjects with lorazepam.
•$p < .05$ (corrected).
Note first the distinction in localization between negative and positive emotions in subjects receiving placebo that is longer present in subjects with lorazepam. Second, the influence of lorazepam on localization of dipoles in both negative and positive emotions is clearly visible.

of relationship as well as underlying physiological mechanisms, which however remain unclear, will be further discussed in the following sections.

In addition to orbito-frontal cortical modulation during emotional processing, results revealed alterations in cortical motor function in subjects receiving lorazepam. One may consequently assume both emotional and motor effects of lorazepam, which however may be difficult to disentangle entirely in physiological terms.

GABA-ergic Modulation of Orbito-Frontal Cortical Emotional Processing

As has been demonstrated in healthy subjects without any application of benzodiazepines (Northoff, Richter, et al., 2000; Mayberg et al., 1999), negative and positive emotional processing led to an almost inverse pattern of concurrent increases and decreases of signals in the orbito-frontal and lateral prefrontal cortex. The orbito-frontal and lateral prefrontal cortex could be characterized by opposite kinds of activity with strong signal increases in one region and concurrent strong signal decreases in the other. Comparing negative and positive emotional processing, one could find an inverse pattern with regard to signal increases and decreases in both regions. Consequently, one may assume that such opposite kinds of activity in the orbito-frontal and lateral prefrontal cortex may be mutually dependent on each other—such an assumption has been supported also by a review of several studies implicating both regions (Drevets & Raichle, 1998). However, mechanisms and functional regulation of such a mutual dependence remain unclear. Since concurrent increases and decreases of signals in the orbito-frontal and lateral prefrontal cortex during emotional processing may be modulated neurochemically by GABA-A receptors, we investigated the influence of lorazepam on these patterns of activity.

Our results reveal that the pattern of signal increases and decreases in the orbito-frontal cortex was reversed almost completely by lorazepam whereas such a reversal was not obtained in the lateral prefrontal cortex. It is this reversal of the pattern of signal increases and decreases rather than the increases/decreases themselves that must apparently be considered as specific for orbito-frontal cortical modulation by lorazepam. Though lorazepam induced signal increases and decreases in other prefrontal cortical regions as well as in the lateral prefrontal and

premotor/motor cortex, such a reversal of the pattern of increases/decreases was observed in the orbito-frontal cortex exclusively. Assumption of specific relationship between orbito-frontal cortical function and GABA-ergic modulation by lorazepam is further supported by the following findings: (1) Absence of any effects of lorazepam on medial prefrontal cortical function; (2) shift of dipole underlying the EMF from orbito-frontal cortex to medial prefrontal cortex in subjects receiving lorazepam.

However, a relationship between orbito-frontal cortical function and GABA-ergic modulation by lorazepam does not necessarily imply that this relationship is specific for emotional processing as in contrast to nonemotional processing. The following results do support the assumption that GABA-ergic modulation in the orbito-frontal cortex may be related rather with emotional processing than with nonemotional processing: (1) Significant alterations in signal increases and decreases in the orbito-frontal cortex in emotional contrasts especially in positive emotions; (2) observation of orbito-frontal cortical reversal of signal increases and decreases (see above) only in emotional conditions (negative and positive) whereas such a reversal could not be obtained in nonemotional (neutral, gray) conditions; (3) change of dipole location in both emotional conditions in subjects receiving lorazepam. One may, however, argue that effects of lorazepam cannot be specifically related with emotional processing since changes in reaction time, premotor/motor cortex, and movement-related magnetic fields occurred in both emotional and nonemotional conditions. These changes concern primarily effects of lorazepam on cortical motor function that may indeed be independent from the kind of processing either emotional or nonemotional (see below for further discussion of these effects). One may consequently distinguish between specific emotional orbito-frontal and nonspecific emotional premotor/motor cortical effects of lorazepam. However, emotional and motor effects of lorazepam may be difficult to disentangle in physiological terms, for example, in case of the lateral prefrontal cortex as being apparently involved in both kinds of effects. Although our results must be considered as preliminary awaiting further empirical confirmation, the present results nevertheless present some evidence for the assumption of particular involvement of orbito-frontal cortical function in emotional effects of lorazepam.

The orbito-frontal cortex, especially its medial part, receives strong afferents from the basal nucleus of the amygdala (Carmichael & Price, 1996; Barbas, 1995; Morecraft, Geula, & Mesulam, 1992; Morecraft & Van Hoesen, 1998), which by itself is closely related to negative emotional processing (Breiter et al., 1996; Damasio, 1997; Irwin et al., 1996, 1997, 1998; Morris et al., 1996, 1998). Both the amygdala and the orbito-frontal cortex show high densities of GABA-A receptors in certain subregions (Carmichael & Price, 1994; Davis & Rainnie Cassell, 1994). Such anatomical and neurochemical features of the orbito-frontal cortex could probably account for relationship between orbito-frontal signals and neurochemical stimulation with the GABA-A potentiator lorazepam during negative and positive emotional stimulation as demonstrated in the present study. In addition, the assumption of such a relationship between orbito-frontal signals and GABA-A receptors is further supported by Vesilis et al. (1998). They demonstrated dose-dependent decrease of rCBF in the orbito-frontal cortex after the application of midazolam (another benzodiazepine more or less similiar to lorazepam) (Veselis et al., 1998).

The exact nature of the relationship between orbito-frontal signals and GABA-A receptors remains unclear since relationship may be either direct or indirect. Assumption of a direct relationship would imply that orbito-frontal cortical signals during emotional processing are directly modulated by GABA-A receptors. GABA-A receptors exert an inhibitory influence on regional cerebral flow (Spanaki et al., 1999; Kelly & McCulloch, 1983) and neuronal activity (Crestani et al., 1999). Therefore, one may assume that lorazepam, as a GABA-A potentiator, may lead to an increase in neuronal inhibition in the orbito-frontal cortex. Assumption of a direct and therefore causal relationship between GABA-A receptors and emotional processing is supported by animal studies showing alteration of neuronal activity in the amygdala, hippocampus, and cortical regions during application of benzodiazepines (Crestani et al., 1999; Kalynchuk, Pearson, Pinel, & Meaney, 1999; Benareha et al., 1998; Corda et al., 1997). In humans, it could be demonstrated that benzodiazepines in healthy subjects lead to alteration in perception and subjective experience of emotions (Ferrara et al., 1999; Garcia et al., 1997). Clinicotherapeutically, benzodiazepines, especially lorazepam, show an almost immediate and dramatic anxiolytic effect in diseases with strong orbito-frontal cortical alterations such as obsessive–compulsive disorder (Coplan & Lydiard, 1998), panic disorder (Gorman, Kent, Sullivan, & Coplan, 2000), and catatonia (Northoff, Wenke, Demisch, & Pflug, 1995; Northoff, in press). The exact relationship between neuronal inhibition and the BOLD effect underlying generation of signals in fMRI remains however unclear since currently the exact relationship of BOLD signal to pre- and postsynaptic mechanisms of neurotransmission is not fully understood (Raichle, 1998). Thus, it is conceivable that increases in fMRI signals may be related to either increased excitatory or inhibitory mechanisms. Since the functional mechanisms between the BOLD effect underlying fMRI signals and GABA-A receptors remain unclear (see Kelly & McCulloch, 1983) the assumption of such a direct, namely, potentially causal relationship between orbito-frontal signals and GABA-A receptors has not been proven in humans yet.

Another potential mechanism by which lorazepam may influence orbito-frontal signals during emotional

processing may be the alteration of regional cerebral perfusion, which, via the BOLD effect, may then alter orbito-frontal signals. It has been demonstrated that the inhibition of GABA-A receptors by picrotoxin, a GABA-A inhibitor, led to an increase in rCBF in rats (Forman et al., 1998). In accordance with these results, lorazepam, as a GABA-A potentiator, and other GABA-ergic drugs lead to the reduction of both regional (especially in the prefrontal cortex) and global cerebral blood flow (Spanaki et al., 1999; Wang et al., 1996; Matthew et al., 1995). Therefore, concomitant investigation of emotional/motor activation, rCBF, and GABA-A receptors would be necessary in order to directly relate orbito-frontal cortical emotional processing with GABA-ergic control in humans.

Alternatively, one may assume an indirect relationship between orbito-frontal cortical signals and GABA-A receptors. For example, lorazepam may modulate neuronal networks implicated in attention as has been demonstrated recently in the case of noradrenaline (Coull, Büchel, Friston, & Frith, 1999). Since lorazepam modulates attentional function (Ferrara et al., 1999), which by themselves may influence emotional processing, such an indirect effect of lorazepam on orbito-frontal cortical signals via attention cannot be excluded. Subjects receiving lorazepam showed peculiarities in the gray–neutral contrast (see Results), which may be related to an altered level of arousal/attention. These effects were predominant in the anterior cingulate, lateral prefrontal cortex, and medial prefrontal cortex, whereas they were not observed in the orbito-frontal cortex (and premotor/motor cortex). Therefore, modulation of the orbito-frontal cortical activity by lorazepam may rather be related with emotional processing than with attentional/arousal effects. Although psychological studies support the assumption of distinct and dissociable effects of lorazepam on emotional, attentional/arousal, and motor function (Ferrara et al., 1999; Garcia et al., 1997; Garcia, Micallef, Philoppot, Jouve, & Blin, 2000), further imaging studies are needed to disentangle the respective underlying anatomo-physiological details.

Another possibility of an indirect relationship between orbito-frontal signals and GABA-A receptors would be GABA-ergic modulation in the occipital cortex where GABA-A receptors show the highest density in the brain (see Northoff et al., 1999; Schröder, Bubeck, & Demisch, 1997). Lorazepam may have bound to GABA-A receptors and thus modulate neuronal activity in the occipital cortex and may then, via functional connectivity, lead to consecutive alterations in signals in the amygdala and orbito-frontal/prefrontal cortex. Since we could not include the occipital cortex in our fMRI measurements we can neither verify nor falsify such an assumption. Other regions such as the brain stem may be involved as well since it shows strong connections to both amygdala and orbito-frontal cortex. Finally, orbito-frontal cortical signals during emotional processing may be primarily modulated by other transmitter systems than GABA, e.g., by serotoninergic (5-HT1a, 5-HT2a, etc.) or glutamatergic (NMDA, Kainat, etc.) receptors that may interact with GABA-A receptors.

GABA-ergic Modulation of Premotor/Motor Cortical Processing

In addition to alterations in orbito-frontal cortical activation/deactivation pattern, we found significant changes in the cortical motor function in subjects receiving lorazepam, which is reflected in the following results: (1) Significantly lower signal increase and decrease in the lateral prefrontal, premotor, and motor cortex in the lorazepam group; (2) significantly reduced strength in movement-related magnetic fields in subjects with lorazepam; (3) significantly longer reaction times in subjects receiving lorazepam than in those with placebo (see Preston, Ward, Broks, Traub, & Stahl, 1989; File & Lister, 1985); (4) significant correlation of reaction times with lateral prefrontal/motor cortical signal decrease and movement magnetic field strength in the lorazepam group. In contrast to orbito-frontal cortical function during lorazepam, these changes in motor function were independent from the kind of condition either emotional or nonemotional.

Cortical motor function including planning, preparation, initiation, and execution of movements has been shown to be closely related with lateral prefrontal, premotor, and motor cortical activity (Jahanshahi et al., 1995). In addition, it has been demonstrated that cortical motor function in these areas can be influenced by benzodiazepines (Northoff, Pfennig, et al., 2000) and are apparently modulated by GABA-ergic neurotransmission (Kubota, 1996; Kurata & Hoffmann, 1994; Hikosaka, Tanaka, Sakamoto, & Iwamura, 1985). Therefore, our finding of alteration of cortical motor function by lorazepam is in full accordance with these results.

Methodological Limitations

First, we applied several strategies to minimize arousal and attention effects, which, however, cannot be excluded entirely in our activation paradigm. Positive, negative, and neutral pictures were matched for content, dominance, and arousal (see Methods). Psychological states as measured with the BFs (see 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 neither be accounted for by increased preexperimental 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 that were associated with the

first and last picture within each block. In addition, we included two nonemotional control conditions, gray and neutral pictures, accounting for potential effects of arousal and attention by visual stimulation. Present fMRI results suggest that emotional effects of lorazepam are reflected predominantly in modulation of orbito-frontal cortical function. In contrast, attentional/arousal effects of lorazepam may rather be related with the anterior cingulate and medial and lateral prefrontal cortex (see above). However, further studies are certainly necessary to disentangle anatomo-physiological details of attentional/arousal and emotional effects of lorazepam.

Second, we did not investigate test–retest reliability, which, due to fast habituation processes as shown in a previous study (Büchel et al., 1998; Whalen et al., 1998; Breiter et al., 1996), may methodologically be problematic. 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 avoiding potential order effects.

Third, measurements in fMRI covered only the frontal lobe whereas other regions of potential interest, for example, the amygdala, could not be included. We used slow but less noisy sequences in fMRI in order to avoid further additional stress as well as interference with emotional stress. The orbito-frontal cortex is close to regions with a high potential for magnetic susceptibility artifact. Given the unpredictable effects on T2-weighted signal change from regions with high susceptibility, we, based on the work of Breiter et al. (1996, 1997), checked and confirmed that the 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 or even higher than the stimulus-correlated activity) they were excluded from analysis. We included only stimulus-correlated variation in signal intensity that is more or less independent of overall signal intensity. In addition, susceptibility artifacts may rather reduce the detection of stimulus-correlated variation in signal intensity, which supports the assumption that orbito-frontal activity as detected in negative emotions could not be accounted for by artifacts. Even if we cannot exclude differences in signal-to-noise ratios between different regions entirely, we nevertheless compared standard deviations of activity between the orbito-frontal cortex and other regions of interest (ROIs). Orbito-frontal activity showed no higher standard deviations than other regions so that there seems to be no major difference in this regard.

Fourth, we found a high proportion of negatively correlated activity in fMRI that 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, or an altered coupling mechanism between oxygen consumption and rCBF. Several PET studies found concomitant increases and decreases in rCBF during emotional stimulation (Drevets & Raichle, 1998; Baker et al., 1997; Lane, Reimann, Ahern, et al., 1997; Lane, Reimann, Bradley, et al., 1997; Paradiso et al., 1997; Reimann et al., 1997; George et al., 1995) so that it seems quite plausible, at least in the present study, to relate such signal decreases as negatively correlated voxels to decreased regional activity in either of the two conditions within the respective contrast. Regions that are activated during negative emotions, for example, the orbito-frontal cortex, may be suppressed (or deactivated) in neural processing of positive pictures and vice versa (see Drevets & Raichle, 1998).

Fifth, we did not explicitly investigate visual attentional functions that could be related to EMFs. However, our findings of considerable differences in strength of EMF between negative and neutral emotional 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 Methods). Eye movements cannot account for EMF since electrooculogram (EOG) was measured in MEG (but not in fMRI; see Methods) with rejection of contaminated electromagnetic signals so that electroocular artifacts were excluded from analysis. In addition, all subjects had to fixate on a central fixation point during the presentation of each picture in MEG and fMRI in order to avoid eye movements. Even if eye movements were present, they would rather lead to activation in the superior medial prefrontal cortex (BA 6 and 8) (Bodis-Wollner et al., 1997; Darby et al., 1996) than in the orbito-frontal and inferior prefrontal cortex as obtained in the present study. Alterations in EEG induced by emotions have been shown in several studies before (Aftanas et al., 1998; Pizzagalli, Koenig, Regard, & Lehmann, 1998; Pihan, Altenmüller, & Ackermann, 1997; Schupp, Cuthbert, Bradley, Birbaumer, & Lang, 1997; Naumann, Bartussek, Diedrich, & Laufer, 1992; Naumann, Bartussek, Diedrich, Vogelbacher, & Mehrtens, 1993), which further support our assumption of a specific relationship of the EMF with emotional stimulation (see also Northoff, Richter, et al., 2000). Nevertheless, the exact interpretation of the EMF remains unclear. Since it occurred 400–500 msec (subtraction of reaction time from the time of onset of the movements, which was used as a trigger) before the appearance of a new picture, one may interpret the EMF as a sort of contingent negative variance (CNV). However, a CNV should have been of longer temporal duration until the appearance of the next picture, which was not the case.

Sixth, in investigating the prefrontal cortical spatio-temporal activation pattern, we combined fMRI and MEG. Techniques with high spatial (fMRI) and high temporal (MEG) resolution have been advantageously combined before (Northoff, Richter, et al., 2000; Heinze

et al., 1994), particularly in movements (Joliot et al., 1998; Stippich et al., 1998; Sanders, Lewine, & Orrison, 1996). Though there are several methodological problems applying two techniques with different neurophysiological substrates, blood oxygenic (fMRI) and electromagnetic (MEG) activity, the above-cited studies have nevertheless shown high coincidence between both kinds of signals (Northoff, Richter, et al., 2000; Joliot et al., 1998; Stippich et al., 1998; Sanders et al., 1996; Heinze et al., 1994). Consequently, combining spatial and temporal measures with fMRI and MEG may further reveal similarities and differences in physiological mechanisms in negative and positive emotional processing. In addition, neurochemical activation studies have been performed successfully in either PET (Veselis et al., 1998) or fMRI (Breiter et al., 1997), demonstrating significant alterations compared to placebo, so that these techniques are apparently sensitive to neurochemical modulation.

METHODS

Subjects

Two groups of healthy controls (each group $n = 8$) with comparable age (means ± *SD*: 25.1 ± 6.2 and 24.7 ± 5.4 years; all right-handed) and sex (four women and four men in each group) were investigated. 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 were excluded. No subject was taking regular medication.

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

Design

Affective Stimulation

Affective stimulation was performed with pictures from the IAPS (Lang et al., 1997), which was validated also on a German population (Hamm & 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) and purely gray (i.e., entirely colored with different tones of gray) pictures served as control conditions in order to control for potentially confounding features of the emotion-generating pictures such as emotionally irrelevant visual stimulation and attentional effects. Slide sets were matched for content/properties (scenery, objects, colors, people, faces, animals), dominance (according to subjective ratings provided by IAPS), and arousal (according to subjective ratings provided by IAPS). Though such matching is not available by the IAPS itself, we nevertheless tried to match pictures as much as possible in accordance with the method applied by Irwin et al. (1997). Even if the same content or scenery was not exactly available in another valence, we nevertheless tried to match the respective picture with a picture containing a somehow related content or scenery. For example, a book was not matched with a picture including people or animals or vice versa. Subsequently, pictures differed only in emotional valence (positive, neutral, negative) but not in dominance or 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 sec, respectively, in blocks with 10 valence constant pictures (positive, negative, neutral, and gray blocks). Between the blocks, there was a break of 3 sec. The order of blocks was counterbalanced with regard to emotional valence as well as between fMRI and MEG 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 sec, 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 so that simple reaction time could be measured (see below).

Paradigm Implementation

For both MRI and MEG, the visual stimuli were projected automatically via a computer and a back-projection television system. Paradigm implementation was similar to the study of Northoff, Pfennig, et al. (2000) and Northoff, Richter, et al. (2000), where they are explained in full detail.

Subject Instruction

The experiment took place in four sessions. Sessions 1 acquainted subjects with the scanners in fMRI and MEG. Sessions 2 and 3 were the actual scanning sessions. The order of investigations (first MEG, then fMRI, or reverse) was counterbalanced for subjects within each group controlling for potential order effects. Fifteen minutes before each investigation, subjects received either placebo (i.e., saline) or lorazepam (i.e., 1 mg) intravenously in a double-blind study design. In both investigations, subjects received the same substance (placebo or lorazepam). Such a design relying on intersubject comparison with regard to the application of placebo and lorazepam in different subjects was chosen in order to

avoid repetition effects concerning picture presentation that could have not been ruled out entirely in a design that relies on intrasubjective comparison since each subject would have then undergone the experiment four times (fMRI and MEG, respectively, before and after lorazepam). In Session 4, subjects made ratings of the pictures to which they were exposed receiving again placebo or lorazepam, respectively.

Prior to all sessions, subjects were told that they would view various pictures with different emotional contents. Furthermore, they were informed that they would receive an intravenous injection before fMRI/MEG to which both they and the experimenters were blind. Injections would either be saline or 1 mg lorazepam. The doses and timing of lorazepam were chosen based on the ability of lorazepam to displace (endogenous or exogenous) ligands from the benzodiazepine subunit of the GABA-A receptor (Schröder et al., 1997) as well as with regard to the therapeutically effective dose in patients with strong and uncontrollable anxieties (Northoff et al., 1998, 1999; Coplan & Lydiard, 1998).

Details of further instructions given in order to avoid motion artifacts, and so on, are explained in Northoff, Richter, et al. (2000) in full detail.

Behavioral, Psychological, and Physiological Monitoring

Behavioral monitoring was accounted for by reaction time. Reaction time was defined as the time subjects needed to press a button (mouse click) as soon as a novel picture appeared on the screen. They had to press the button without making any further decision about the nature of the stimuli by emotion so that we measured simple reaction time. For analysis, we calculated the means of reaction time for each condition (i.e., positive, negative, neutral, gray) and compared them statistically using Friedman and Wilcoxon tests for dependent samples. We chose reaction time as a behavioral measure for emotional valence and effect of lorazepam. It is known that the time necessary for movement preparation and initiation depends on the respective functional context (other movements, concomitant visual stimuli, etc.), the more complex the content (and the movement), the longer the reaction time (Naito et al., 1998; Kristeva, Cheyne, & Deecke, 1991; Kristeva-Feige et al., 1997). Hence, we expected differences in reaction times among 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 $p = .0042$). In addition, it is known that lorazepam prolongs reaction times (Preston et al., 1989; File & Lister, 1985) so that reaction time can be used as a behavioral measure of the effect of lorazepam.

In order to control for preexperimental psychological states, which might influence emotional induction, all subjects had to fill out the BFs (Zerssen, 1976), a well-validated instrument for self-evaluation of the actual psychological state.

Pictures from the IAPS were subjectively rated for valence, dominance, and arousal with the Self-Assessment Manikin (Lang et al., 1997). Ratings of IAPS were done after fMRI/MEG investigations. Subjective ratings of the different conditions were compared with those obtained by Lang et al. (1997), which were also validated for a German population (Hamm & Vaitl, 1993).

Effects of lorazepam/placebo were monitored both psychologically and neurochemically during the later rating session. We used the Covi Anxiety Scale (Goldberg & Finnerty, 1982) for psychological monitoring before and after (10, 20, 30, 45, and 60 min postinjection) the application of lorazepam/placebo. Neurochemically, serum concentrations of lorazepam (according to the method by Greenblatt, Franke, & Shader, 1978), cortisol, and growth hormone were measured before and after (10, 20, 30, 45, and 60 min postinjection) the application of lorazepam during the later rating session in order to correlate them with psychological effects. Cortisol and growth hormone were determined since it is known that both are influenced by benzodiazepines (increase of growth hormone, decrease of cortisol; Hommer et al., 1986). For interindividual comparisons, scores in the Covi-Anxiety Scale and serum levels of lorazepam, cortisol, and growth hormone are given as the percent change of the respective score/level obtained before lorazepam/placebo administration. For data analysis, integrals of the respective values were calculated such that baselines (before lorazepam/placebo) and alterations after lorazepam/placebo (in percent change) could be compared between both groups.

Due to the influence of magnetic fields in MEG/fMRI, we were unfortunately unable to obtain vegetative measures of emotional responses (skin resistance, etc.) during scanning. Only the heart rate, showing no significant differences between conditions and groups (mean heart rate during scanning, that is, 45 min: 73.3 ± 4.5 min in negative pictures; 69.5 ± 3.6 in positive pictures; 68.8 ± 3.8 min in neutral pictures; 62.3 ± 3.6 min in gray pictures) could be obtained during MEG but not during fMRI.

fMRI

Data Acquisition

The images were acquired in a Bruker Biospec 3-T/60-cm 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 the MEG to the anatomical and fMRI 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 dB A), low-contrast FLASH images in sagittal and coronal 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 orbito-frontal cortex, and the anterior cingulate (i.e., from orbito-frontal 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 × 64 matrix size) (see Figure 1). Two hundred forty functional images for each slice were collected using a low-noise conventional gradient-echo sequence (SPL, 58 dB A; TE, 40 msec; TR, 313 msec; flip angle, 8°) with medium high resolution (2.5 × 2.5 × 8 mm) within 45 min. For each block of visual stimuli (i.e., 10 valence constant pictures each presented for 6 sec 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 sec), resulting in a total acquisition time of 1 min (i.e., 6 × 10 sec) 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, an acquisition time of 40 min, and, due to breaks between blocks, a total duration of 45 min.

High T1-contrast imaging (MDEFT) was used to obtain anatomical landmarks with 3-D high resolution and immediately followed fMRI with the following parameters: 256 mm field of view, 2.25 mm slice thickness, 64 slices, and 256 × 256 in-plane matrix size. On the basis of these anatomical images, the localization of slices/activity in fMRI and dipoles from MEG were determined.

Image and Statistical Analyses

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. Based on the standard (Sanders et al., 1996; Bandettini, Jesmanowicz, Wong, & Hyde, 1993), subjects with head movements >2 mm and or >1° were excluded from initial analysis. We unfortunately had to exclude two persons (one receiving lorazepam, one receiving placebo) from analysis that finally included eight subjects with lorazepam and eight subjects with placebo as described above. In order to exclude eye movement artifacts (see Lang et al., 1998; Irwin et al., 1997), we finally checked vertical and horizontal EOG as measured in MEG (see below) in all subjects. None of the subjects entering final analysis showed any eye movements in EOG (see Figure 5).

All subjects entering into final and statistical analysis were checked for eye movements artifacts (see Irwin et al., 1997) as revealed in vertical and horizontal EOG as measured in MEG. None of the subjects entering final analysis showed any eye movement artifacts (see Figure 4). Second, activation analysis was performed by computing the correlation coefficients between voxel time response and boxcar waveform representing the stimulation. Irrespective of their actual serial position in the sequence, all negative and positive blocks were modeled as ''on,'' whereas all neutral and gray blocks were defined as ''off.'' Voxels having correlation coefficients with a statistical significance $p > .01$ (corrected) were rejected. Then the functional images were superimposed on the individual anatomic reference images (Gaschler-Markewski et al., 1997).

In each slice, different anatomical ROIs were outlined on the respective anatomical MRI without separate functional overlay for each individual subject. For each subject, 11 brain regions (see Figure 1) were defined individually by landmarks (i.e., the respective gyri with upper orbital gyrus, inferior, middle, and superior frontal gyri, cingulate gyrus, and medial frontal gyrus) and manually delineated on the T1-weighted images (see Kammer et al., 1997, for a similar method). Fiducial marks were then made on the anterior and posterior commissures, midsaggital point, and on the most anterior, posterior, superior, inferior, left, and right points of the brain that were used to standardize each participant's anatomy in a normalized space so that the various brain regions could be identified based on the atlas of Talairach and Tournoux (1988) and characterized by the corresponding Brodmann's areas. The corresponding regions on adjacent slices were aggregated and then defined as the upper part (exclusion of lower part) of the orbito-frontal cortex (BA upper 11 and 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 (see Kammer et al., 1997, for a similar method). Since the orbito-frontal cortex is close to regions with a high potential for magnetic susceptibility artifacts, we, based on Breiter et al. (1996, 1997), checked that orbito-frontal activations did not overlap regions of susceptibility artifact, otherwise (i.e., if artifacts were as high or even higher than stimulus-correlated activity) they were excluded from analysis ($n = 2$, which were identical with those excluded on the basis of movement artifacts; see above) so that the number of placebo subjects ($n = 8$) and lorazepam subjects ($n = 8$) entering into final analyses was not further reduced by analysis of susceptibility

artifacts (see also methodological limitations). Even if the determination of ROIs according to Talairach and Tournoux (1988) 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, making our localizations comparable with other studies. In addition, the determination of ROIs 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. Then these functional t maps were thresholded ($Z = 3.09$ or $p < .01$, corrected for multiple comparisons) and constrained to include four contiguous voxels in the final map, which effectively reduces the rate of false positives. Constraining the final maps on the basis of cluster size allows fMRI analyses to control for multiple comparisons without the concomitant loss of power that would occur with a Bonferroni correction method. Finally, t statistic maps were overlaid onto our anatomical template image to attribute each activation focus to an anatomical area. The number of voxels and the percentages of significantly activated voxels and IWV (product of the absolute number of voxels and average signal change in each ROI in all slices) were determined for positive (positive IWV probably reflecting activation) and negative (negative IWV probably reflecting deactivation; see Methodological Limitations) correlated activations (Gaschler-Markewski et al., 1997). The number of voxels and IWVs were calculated for each region for every individual subject in all conditions, which then entered into statistical analyses for comparison of conditions between groups and correlation analyses (with reaction times) as described below in further detail (see Statistical Analyses).

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. The 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 EOGs from both eyes. Surface EMG associated with abduction of the index finger was recorded from two electrodes placed about 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. The position and orientation of the sensor as well as the head shape with respect to this coordinate system were measured with a 3-D 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-sec duration (1,800 msec pretrigger interval). Offline reduction of environmental noise was performed through subtraction of the weighted signals from three reference channels. Automatic rejection level of field amplitudes larger than 3 pT/cm was used for excluding magnetic artifacts; for EOG, the rejection level was 100 μV. 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 Notzh filter.

Off-Line Analysis of Data

Signals as obtained in MEG and filtered in the above-explained way were analyzed off-line in order to generate isocontour maps and source identification relying on a single-dipole model (see Northoff, Richter, et al., 2000, for details).

First, all trials were visually inspected for artifacts (ocular, other movements, etc.) so that only those trials containing movements with the same abrupt onset rise time and the same shape as seen on EMG were utilized for further analyses. A total of at least 70 artifact-free trials for averaged for each conditions, respectively. There were no significant differences between conditions in terms of artifacts.

Second, after digital low-pass filtering at 45 Hz and a 50-Hz Notzh filter, the signals were subjected to amplitude measurements within epochs of 50 msec within a time window of analyses of 2200 msec (−2000–200 msec), of which the first 200 msec were used for determining the baseline. These data were used for the construction of isocontour maps and dipole source location. Thereby,

occipital channels were excluded for analyses in order to avoid interference between visuo-emotional processing in the visual regions (see Lang et al., 1998) and early emotional processing in the prefrontal cortex.

Third, isocontour maps of the field amplitude were constructed at the above-selected latencies using linear interpolation. To identify underlying sources signal distributions were modeled using the model of moving dipole (MD) embedded in a homogenous spherical volume conductor. The center of the volume conductor was evaluated by approximating the surface of the scalp underneath the gradiometer system by the abovementioned sphere. The model parameters (strength, position, and orientation) were optimized by means of an iterative least-square procedure. The MD analyses were performed for each 50-msec epoch within the time window of analyses. Only MDs accounting for 60% of the field variance and with a GOF value >85–90% were accepted. For each 50-msec epoch within the time window of analyses, the MD with the best GOF value was taken as the representative one.

Fourth, dipole locations were projected onto the corresponding three-dimensional anatomical MRI that was marked (nitro capsules) by three markers (nasion, both preauricular points). These markers could be easily identified in MRI and serve as reference points for the localization of estimated dipole locations. Functional images were matched on anatomical images as well to compare anatomical localization between dipoles and fMRI signals. The nearest local maximum (as described in millimeter) between dipole and fMRI signal was determined based on the method described by Sanders et al. (1996).

Statistical Analyses

Comparison Between Groups

Statistical analyses of the various fMRI and MEG parameters between conditions within groups (i.e., comparison of conditions within each group) as well as between groups within conditions (comparison of each condition between groups) were made with Kruskal–Wallis/Friedman analysis and Mann–Whitney *U*/Wilcoxon tests applying Bonferroni correction for multiple comparisons. In addition, we performed MANOVA with two factors concerning group (placebo, lorazepam) and region.

Correlation Between Variables

First, in an exploratory way, we correlated regional activities in fMRI and amplitudes and latencies in MEG with behavioral measures using Spearman correlation with Bonferroni correction for multiple comparisons. Following the recommendations by Curtin and Schulz (1998), only those fMRI/MEG parameters were selected for correlational analyses that showed significant differences between both groups in order to reduce the number of comparisons. Second, we performed partial correlations to control for effects of age on those tests for which correlations were significant since increases and decreases of signals during emotional processing may be age-dependent (Lane, Reimann, Ahern, et al., 1997; Lane, Reimann, Bradley, et al., 1997; Lang et al., 1997). If correlations turned out to be significant in both kinds of analyses (i.e., we found no differences in numbers and kind of relations between correlation and partial correlation), they were considered as relevant relationships between variables so that only these are mentioned in the Results section.

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The data reported in this experiment have been deposited in the fMRI Data Center (http://www.fmridc.org). The accession number is 2-2001-112D3.

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