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Lorazepam modulates orbitofrontal signal changes during emotional processing in catatonia

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Objective Catatonia is a psychomotor syndrome characterized by concomitant emotional, behavioural and motor symptoms. In many cases clinical symptoms disappear almost immediately with administration of lorazepam, which acts on $GABA_A$ receptors.
Methods Using functional magnetic resonance imaging (fMRI) we investigated prefrontal activation patterns during emotion processing in catatonic patients with and without lorazepam in a double-blind study design. For emotional stimulation the International Affective Picture System (IAPS) was used. BOLD-signals were determined using regions of interest (ROI) and were statistically compared between groups.
Results For negative emotional pictures lorazepam induced higher signal decreases in the orbitofrontal cortex (OFC) in catatonic patients than in healthy subjects resulting in a regularization of activity patterns comparable to healthy subjects with placebo.
Conclusions Results indicate disturbances in the functioning of OFC in catatonia. GABAergic modified emotion regulation with decreased inhibition of affective stimuli could lead to the intense emotions reported by many catatonic patients.

KEY WORDS — catatonia; affect; fMRI; benzodiazepine

INTRODUCTION

Catatonia is a psychomotor syndrome characterized by concomitant emotional (anxieties, depression, mania), behavioural (mutism, stupor, stereotypes, perseveration) and motor (akinesia, posturing, catalepsy) symptoms (Bush *et al*., 1996; Fink and Taylor, 2001). Unlike patients suffering from primary motor disturbances like Parkinson's disease, catatonic patients report intense and uncontrollable anxieties rather than a feeling of inability to move (Northoff *et al*., 1998). Consequently, 60–80% of catatonic patients show symptom improvement when treated with lorazepam, a benzodiazepine with strong anxiolytic properties (Bush *et al*., 1996; Fink and Taylor, 2001).

Neural mechanisms of psychomotor alterations in catatonia still remain unclear. There is no evidence for alterations in the primary motor cortex or supplementary motor area (Northoff *et al*., 1999a). Instead, neural activity in medial and lateral prefrontal cortex is modified during rest in patients with catatonia compared to non-catatonic psychiatric patients (De Tiege *et al*., 2003; Galynker *et al*., 1997; Northoff *et al*., 2004; Satoh *et al*., 1993). Prefrontal regions are part of neural networks involved in emotion processing and are found to be active during the regulation of a motor response to emotional stimuli (Northoff *et al*., 2002). Recently, we showed that anxiety plays a specific role in catatonia (Northoff *et al*., 1998). Therefore disturbances in frontal and prefrontal cortical functions could lead to irregular emotion processing and a higher incidence for catatonic episodes characterized by a 'scared stiff' appearance (Moskowitz, 2004). We were also able to show that negative emotional stimulation in catatonic patients leads to changes in rCBF in medial orbitofrontal cortex (OFC) (Northoff *et al*., 2004). Due to the anxiolytic properties of drugs potentiating $GABA_A$ receptors mediated inhibition, and the high density of $GABA_A$ receptors in the OFC (Davis *et al*., 1994), these alterations may be linked to dysfunctions in GABA-related neurotransmission. The clinical observation that catatonic patients are less sedated than comparable psychiatric patients and show partially remitted emotional and motor symptoms after administration of lorazepam supports the hypothesis of alterations in

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orbito- and midline prefrontal areas. The GABAergic modulation of emotion processing in orbitofrontal and prefrontal cortex has been demonstrated in a functional magnetic resonance imaging (fMRI) study with healthy subjects (Northoff *et al*., 2002), but never with catatonic patients. We therefore investigated prefrontal activation patterns during emotion processing in patients after full remission of catatonic episodes with and without lorazepam compared to healthy controls in a double-blind placebo-controlled study design using fMRI.

MATERIALS AND METHODS

Subjects

A total of six catatonic patients were recruited from the inpatient Department of Psychiatry at the Otto-von-Guericke University of Magdeburg (1 man; age: 41.6 ± 5.3 years [means ± SD]; right-handed; Table 1). Patients with neurological or other physical illnesses, alcohol or substance abuse, or neuroleptic-induced hypokinesias were excluded. Ethical approval and permission were obtained from the Ethics Committee at the University of Magdeburg. After complete and detailed description of the study written informed consent was also obtained from the patients.

Diagnosis was made according to DSM IV and three patients with Catatonic Schizophrenia and three patients with Bipolar I Disorder were included. General clinical symptoms were assessed with various clinical tools (Table 1). Catatonic syndrome was diagnosed according to criteria developed by Lohr and Wisniewski (1987), Bush *et al*. (1996), Rosebush *et al*. (1990) and Northoff *et al*. (1999b). All patients were classified as akinetic and complete akinesia had to last for at least 30 min. Hyperkinetic catatonic patients were excluded, because the two types of catatonia may differ in their neuronal mechanisms. Patients had not taken any benzodiazepines in the last 6 months prior to admission. On admission a dose of lorazepam 1–2.5 mg was administrated intravenously 2–4 times (means: 5.2 ± 1.3 mg).

Table 1. Clinical and demographic data [means ± SD (minimum–maximum)] in catatonic patients

Clinical and demographic data in catatonic patients	
Diagnosis DSM IV	295.20 (n = 3)
	296.53 (n = 3)
Duration of illness (in years)	7 ± 3.85 (2–11)
	28.83 ± 7.44 (18–38)
Age of onset	
Time since episode onset (in weeks)	5.33 ± 1.75 (3–8)
Duration of treatment (in years)	6 ± 3.58 (2–11)
Neuroleptics (CPZ) (in mg)	198.3 ± 188.3 (0–460)
Anticholinergic agents (n of treated patients)	0.67 ± 0.52 (0–1)
Global Assessment Scale (GAS)	16.17 ± 2.14 (12–18)
Positive And Negative Symptom Scale (PANSS)	100 ± 22.1 (80–140)
Hamilton Anxiety Scale (HAM-A)	23 ± 2.19 (19–25)
Depression Scale (HAM-D)	12.67 ± 4.18 (8–20)
Number of catatonic episodes	3.33 ± 2.34 (2–8)
Days of catatonic symptoms	18.83 ± 5.42 (9–25)
Rosebush – Scale	10.67 ± 0.82 (10–12)
Northoff Catatonia Scale:	
NCS – MOT (motor)	21.67 ± 2.66 (18–24)
NCS – AFF (affective)	22 ± 2.19 (20–24)
NCS – BEHAV (behavioural)	25.33 ± 8.82 (10–34)
NCS – TOT (total)	69 ± 11.5 (48–78)

Using the criteria of Rosebush *et al*. (1990), clinical response in a 24 h time period after administration of lorazepam was evaluated and only short-term responders were included in the study. After full remission of catatonic symptoms, lorazepam administration was ceased and patients received either antidepressants or neuroleptics until the fMRI investigation. All patients were remitted from catatonia and not in an acute akinetic state at the time of fMRI investigation. No serum concentration of lorazepam was detected in any of the patients on the day of investigation. A more detailed description of the procedure has already been published elsewhere, together with data after administration of the placebo (Northoff *et al*., 2004). The fMRI investigation took place in a random sequence of placebo and lorazepam. Fifteen minutes before each investigation, subjects received either placebo (i.e. saline) or 1 mg lorazepam intravenously in a double-blind study design (Figure 1).

In the control group healthy subjects received placebo ($n = 8$) or lorazepam ($n = 8$) in a double-blind study design. Unlike catatonic patients the subjects in this group underwent fMRI investigation only once, with placebo or lorazepam. The demographical data and further methodological details are specified in our previous report on emotional processing in the healthy subjects (Northoff *et al*., 2002).

Paradigm

Affective stimulation was conducted with the International Affective Picture System (IAPS) (Lang *et al*., 1993). Negative or positive pictures were matched for content, dominance and arousal and neutral pictures and different tones of grey served as control conditions. Each picture was presented for 6 s only once per experiment, 10 pictures of the same condition were combined into a block, which accordingly lasted 1 min. Altogether, 10 blocks of each condition were presented resulting in a total of 40 blocks. A break of a few

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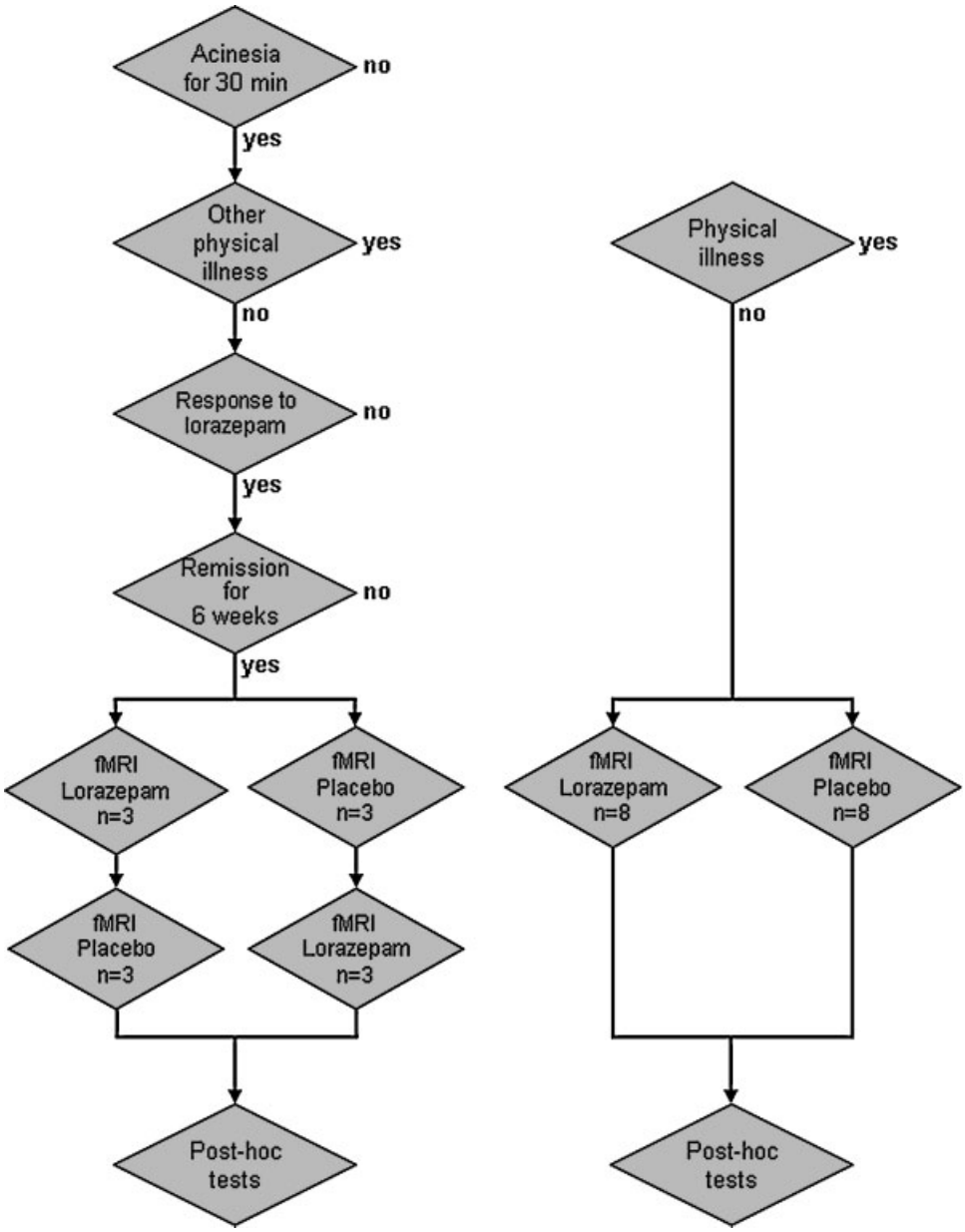

Figure 1. Flow chart summarizing the experimental procedure in the study. After full remission catatonic patients were investigated twice, with lorazepam and placebo in a random sequence

seconds was included between blocks. Subjects were informed that a selection of pictures with different emotional content would be presented and they were to press a touch switch as soon as a new picture appeared. All subjects understood that they could terminate the experiment at any time without further explanation.

The time between the appearance of a new picture and the subsequent button-press was recorded. Reaction times for the different conditions were analysed in a multivariate ANOVA with the factors group (i.e. healthy subjects, catatonia), drug (i.e. placebo, lorazepam) and condition (i.e. positive, negative, neutral, grey). Statistical inferences between groups were made using one-way ANOVA followed by a Bonferroni's multiple comparison test. Further, the time course of reaction times was checked using *t*-tests. All subjects filled out the German-language questionnaire Bf-S (Zerssen, 1976). This scale measures general well being in order to control for potential differences in psychological existential orientation which might influence emotional induction. Pictures from the IAPS were subjectively rated with the Self-Assessment Manikin (SAM) (Lang *et al*., 1993) after the fMRI investigation.

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Functional MRI

The visual stimuli were projected automatically via a back projection television system. Subjects could view the pictures inside the scanner using a binocular triangular prism. fMRI measurements were performed on a Bruker Biospec 3 T/60 cm scanner equipped with a standard birdcage head coil. Initially, a three-dimensional T1-weighted anatomical scan was obtained for structural reference (FOV 256 mm, ISI 2.25 mm, 64 slices, 256×256 in-plane matrix size). Then the following acquisition parameters were used in the fMRI protocol: TR = 240 ms, TE = 40 ms, Flip angle = 8°, ISI 8 mm, FOV $160 \times 160\,mm^2$, 64×64 matrix size. The use of a FLASH-sequence offers the possibility to slow down the gradient switching and allows a 'low noise' imaging sequence (58 dB SPL). Five contiguous axial slices were placed along the anterior–posterior commissure (AC–PC) plane covering the entire frontal lobe. A small field of view was used in order to reduce the number of encoding steps. For each block of pictures six images were acquired, resulting in a total of 240 images.

Functional MRI data analysis

Data were analysed for each subject separately using the software package KHOROS 2.1 with the extension KHORFU (Gaschler-Markefski *et al*., 1997). Functional image sequences were controlled for motion artefacts and shifts in the time course. A correlation matrix between the time series of each voxel and a boxcar waveform representing the picture blocks with positive or negative condition as 'on' and neutral or grey condition as 'off' was calculated. Each voxel with a correlation below 95% level of significance ($p < 0.05$) was rejected. The functional images were then overlaid on the corresponding anatomical scans. In a third step regions of interest (ROI) were defined for further analysis of signal changes and inferences about group effects. Landmarks on the anterior and posterior commissure and other vertices (midsagittal, anterior, posterior, lateral, superior) were used to standardize the volumes and to identify anatomical structures and corresponding Brodmann areas (BA) with the Talairach atlas (Talairach and Tournoux, 1988). For each subject, 11 brain regions were defined (see Figure 3 for further details). The activity in these ROIs was analysed by correlation analysis and thresholded ($z = 3.09$ or $p < 0.01$ corrected for multiple comparisons based on Lang *et al*., 1998) to obtain statistical parametric maps for the different contrasts. Then, percentages of significantly activated voxels were determined and the product of the absolute number of voxels and average signal change in each ROI in all slices (intensity-weighted volumes, IWV) was calculated for positively and negatively correlated activations (Gaschler-Markefski *et al*., 1997). Positively correlated voxels (e.g. positive IWV) probably reflect activation and negatively correlated voxels (e.g. negative IWV) probably reflect deactivation (Gaschler-Markefski *et al*., 1997). Finally the number of IWV was normalized for each subject based on the total number of IWV, and then calculated for each region and each subject in all conditions, which was then entered into statistical analyses. For comparisons between groups (e.g. comparison of catatonic patients with healthy subjects during negative emotional stimulation, with lorazepam) non-parametric Mann–Whitney *U*-tests were performed. To compare catatonic patients within group (e.g. comparison of catatonic patients during negative emotional stimulation with lorazepam or placebo) parametric Wilcoxon tests were used, because catatonic patients underwent the experiment once with and once without lorazepam.

Table 2. Mean reaction times of catatonic patients and healthy controls in ms for the neutral, positive and negative conditions

		Placebo	Lorazepam
Healthy controls	Neutral	533 ± 74	769 ± 82
	Negative	516 ± 64	848 ± 130
	Positive	521 ± 77	785 ± 98
Catatonia	Neutral	881 ± 280[a]	1076 ± 240[a]
	Negative	902 ± 305[a]	996 ± 269
	Positive	851 ± 277[a]	1000 ± 219

[a]Significant differences between catatonic patients and healthy controls for the different conditions are indicated.

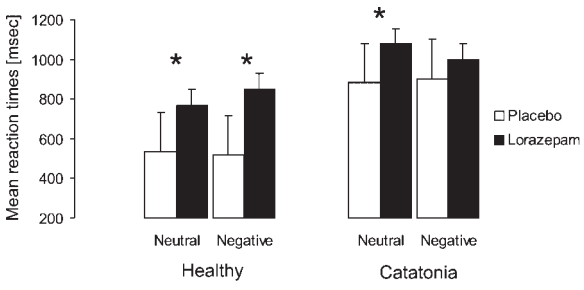

Figure 2. Mean reaction times of catatonic patients and healthy controls for the neutral and negative conditions. Significant differences ($p < 0.05$) between placebo and lorazepam in the within-group comparison are indicated. Note the lack of significance between catatonic subjects with and without lorazepam in the negative condition

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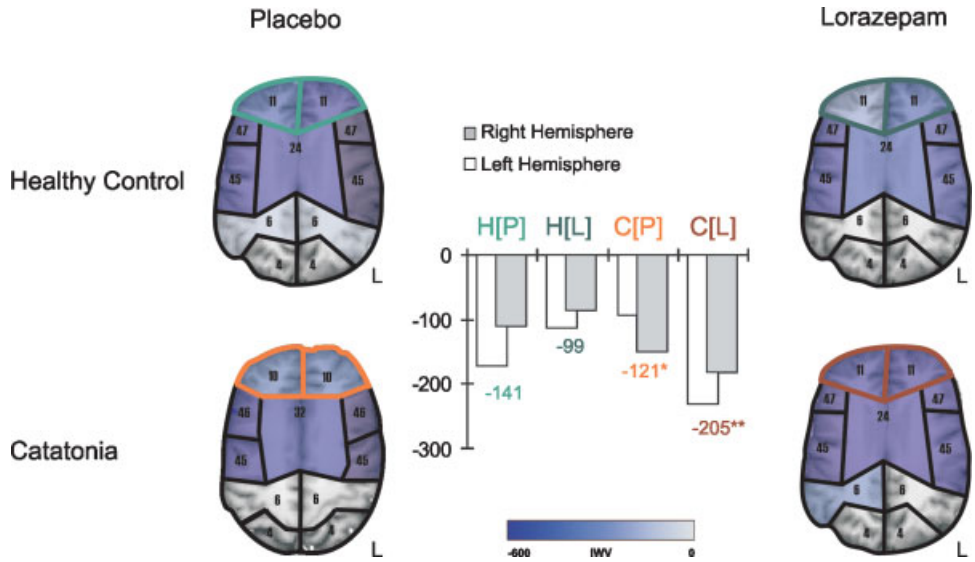

Figure 3. Different ROIs characterized by Brodmann areas (BA) are overlaid as examples on the first or second anatomical slice through the frontal cortex. The areas covered are the upper part of OFC (BA 11, 12), the subgenual anterior cingulate cortex (BA 24, 32), the MPFC (BA 8, 9, 10), lateral prefrontal cortex (BA 9, 45, 46, 47), motor cortex (BA 4) and PMC (BA 6) bilaterally. Signal changes for the contrast Negative > Neutral after administration of lorazepam are shown as IWV for every single ROI. Signal decreases for OFC are also shown as a scale bar in the centre of the figure and significant differences between catatonia and healthy subjects are indicated ($^{*}p < 0.05$, $^{**}p < 0.001$). Note the higher signal decrease during negative emotions in catatonic patients with lorazepam in the OFC, cingulate cortex, MPFC and PMC. Moreover, despite a difference in left and right orbitofrontal signal decrease is obviously in the presented bar diagram, no significant statistical difference was found

RESULTS

Behavioural data

Mean reaction times (RT) in catatonic patients with placebo were significantly higher compared to those in healthy controls with placebo in both negative ($F = 7.85$; $p = 0.004$) and neutral pictures ($F = 7.10$; $p = 0.005$). The same was observed after lorazepam in the case of neutral pictures ($F = 5.21$; $p = 0.046$) while, in contrast, this was no longer the case in negative pictures (Table 2). In contrast to all other conditions, within-group comparison between placebo and lorazepam in catatonic patients was not significant in negative pictures (Figure 2). However, within-group comparison between placebo and lorazepam in healthy subjects show significant differences in all three emotional conditions. This indicates that lorazepam had a specific effect on reaction times in catatonic patients viewing negative pictures.

Pre-experimental psychological states as measured with the Bf-S did not differ significantly between the two groups, though catatonic patients showed higher values (20.0 ± 9.5) than healthy controls (13.3 ± 5.0) indicating increased stress and arousal. Ratings of valence, dominance and arousal of pictures from IAPS did not differ from standard population ratings, indicating no differences in emotional perception, attention, or arousal.

fMRI data

Our first focus was signal decrease in the OFC during negative stimuli (Negative > Neutral). Unluckily we found, perhaps due to low statistical power, no significant differences between the left and right hemispheres. In healthy subjects, lorazepam induced lower signal decreases in the OFC when compared to placebo (see Figures 3 and 4). Catatonic patients, in contrast, showed higher signal decreases in the OFC (see Figure 3) after administration of lorazepam. The pattern of signal decreases in the medial prefrontal cortex (MPFC) and premotor cortex (PMC) resembles the pattern of signal changes in OFC. After administration of lorazepam we found strong signal decreases in these regions in catatonic patients and only weak signal decreases in healthy subjects (see Figure 4).

The above-mentioned findings in OFC, MPFC and PMC could not be observed in the LPFC and MC. Unlike with negative emotional stimuli, administration of lorazepam did not lead to major differences between catatonic patients and healthy controls in positive emotional stimuli. Finally, there were no major

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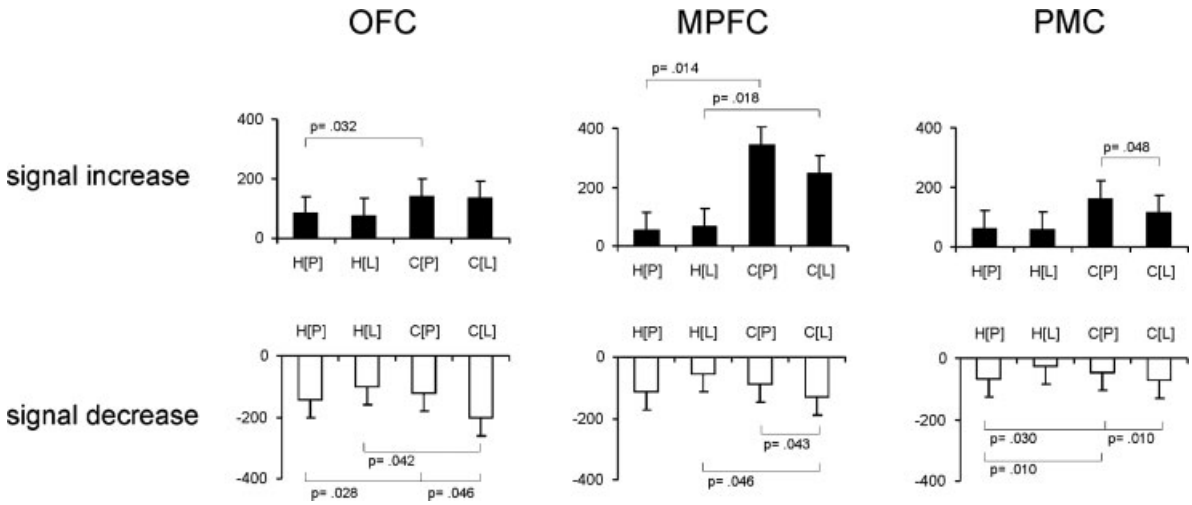

Figure 4. Mean IWV during negative emotion processing for OFC, MPFC and PMC in healthy subjects with placebo (H[P]) and lorazepam (H[L]) (Northoff *et al*., 2002), catatonic patients with placebo (C[P]) and lorazepam (C[L]). Bars for signal increases are black and for signal decreases are white. Significant differences between groups are indicated. Note the same pattern of signal decreases in all cortex areas shown

differences in the Grey > Neutral contrast between catatonic patients with lorazepam and healthy controls with lorazepam, which argues against lorazepam-induced attentional differences in fMRI.

DISCUSSION

This study investigated the modulation of medial prefrontal and frontal activation patterns by lorazepam during emotion processing in catatonic patients. Lorazepam induced higher signal decreases in OFC and MPFC as well as in PMC in catatonia during negative emotional stimulation. These results support the initial hypothesis of abnormal GABAergic modulation of emotion processing in orbitofrontal and prefrontal cortex in catatonia.

The importance of the OFC during the processing of emotional stimuli is well known in healthy subjects and has been validated in a number of studies focussing on rCBF (Phan *et al*., 2002). As reported in our previous publication, catatonic patients show a distinct pattern of orbitofrontal signal changes with stronger signal increase and reduced signal decrease during negative emotions compared to healthy subjects (Northoff *et al*., 2004). Therefore, considering the activation pattern during negative emotion processing in healthy subjects, a pathological inverse activation pattern in OFC could be reasoned. The OFC, especially the medial part, has been shown to be involved in the control and inhibition of emotional associations with visual stimuli (Northoff *et al*., 2004). It is reciprocally and strongly connected with the amygdala, which has been shown to be activated particularly during negative (but not during positive) emotional stimulation (Ledoux, 2000). The OFC seems to regulate and classify incoming emotional stimuli, and a malfunction of this area could lead to decreased inhibition of affective stimuli and therefore to 'unfiltered' intense emotions (Northoff *et al*., 2004). Furthermore, the OFC is well known to be activated in emotion processing and is thought to be especially involved in regulating the awareness of emotions and their appropriate contextual intensity (Phan *et al*., 2002). Moreover, an increased activation of the OFC in depressives compared to remitted depressives and healthy controls is well validated in a number of studies (Drevets, 2007). Catatonic patients have been shown to suffer from intense and often uncontrollable anxieties, which may reinforce the generation of catatonic motor symptoms (Northoff *et al*., 1998). In this sense, catatonic symptoms represent a kind of 'death feint' (Moskowitz, 2004). Our results, combined with previous studies (Northoff *et al*., 2004) and data from the literature (Drevets, 2007; Ledoux, 2000; Moskowitz, 2004; Phan *et al*., 2002), strongly suggest that malfunction of OFC areas and therefore altered emotional processing may at least partially predispose to catatonic episodes. Administration of benzodiazepines has been previously studied with fMRI (Paulus *et al*., 2005) or PET (Veselis *et al*., 1997; Wang *et al*., 1998). The signal decrease in our experiment, particularly in the OFC, was differentially modulated by lorazepam in catatonic patients compared to healthy controls. In healthy subjects lorazepam led, during negative emotion processing, to

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weaker signal decrease (Northoff *et al*., 2002), whereas catatonic patients on lorazepam showed stronger signal decrease compared to placebo. One may therefore assume abnormal GABAergic regulation of the orbitofrontal cortical function in catatonia. Interestingly, the haemodynamic activation pattern in the OFC during emotional processing in catatonic patients after administration of lorazepam resembles that in healthy subjects with placebo. Eventually, the modulation of orbitofrontal activity with lorazepam, which activates GABA transmission, leads to a recovery of emotion regulatory functions in catatonia. In this context, it has to be considered, that the fast recovery of catatonic symptoms in some patients after administration of intravenous lorazepam (Bush *et al*., 1996) might reflect a relationship between GABAergic effects, phenomenology and orbitofrontal dysfunction. The OFC and the amygdala show high densities of GABA-A receptors (Davis *et al*., 1994; Veselis *et al*., 1997) and network interactions relating mediofrontal structures and the amygdala have been modulated with benzodiazepine receptor agonists in animal models (Stevenson *et al*., 2007). Speculatively, lorazepam may thus reverse the acute catatonic state through an increase of GABAergic inhibition in the regulatory circuits mentioned above. This hypothesis is further supported by the close relationship between enhanced behavioural inhibition towards natural aversive stimuli and modulation of GABA-A receptors in prefrontal cortical regions found in animal models (Crestani *et al*., 1999) as well as a higher neuronal density of GABA receptors in the mediofrontal cortex of patients with mood disorders (Bielau *et al*., 2007). However, further studies are necessary to elucidate the exact mechanisms of the effects of lorazepam in catatonia.

Some limitations should be considered in the interpretation of our findings. The reported data must be considered as preliminary due to the small sample size. Despite this problem statistically significant differences between study groups were observed. In order to avoid habituation effects of emotional stimuli, we investigated two different groups of healthy subjects. Unfortunately, due to the rarity of catatonia in general and the even greater rarity of fMRI-eligible catatonic patients, we were not able to investigate two different catatonic subject groups so that the same patients received placebo once and lorazepam once. Therefore, the within-subjects design could lead to greater power in the analysis of signal changes in catatonic patients. However, results showed not only stronger signal changes, but also an inverse pattern of activation compared to healthy subjects. The absence of a control group with psychiatric patients is another severe limitation. In our former studies (Northoff *et al*., 2004) we showed, that no differences in the orbitofrontal activation pattern in fMRI could be found between healthy subjects and psychiatric control patients without catatonia. The psychiatric control patients showed no significant differences in any clinical variable except the presence/absence of catatonic symptoms and no significant differences in reaction times compared to patients with catatonia. However, further studies are urgently needed to elucidate the link between frontal brain function, GABAergic modulation of emotion processing, mood disorders and catatonia. We found a high proportion of negatively correlated signals in fMRI. Several other studies also show a deactivation pattern in prefrontal areas during emotional processing (Baker *et al*., 1997; Mayberg *et al*., 1999). Lorazepam could strengthen negatively correlated BOLD-signals as has been described with barbiturates in narcotic doses (Martin *et al*., 2000). This interpretation seems unlikely though, since catatonic patients with lorazepam showed no prolonged reaction time in negative emotions and were less sedated compared to healthy subjects. The coherence between neuronal activity and an inverse correlation between BOLD signal and stimuli has been extensively discussed elsewhere (Gusnard *et al*., 2001; Hutchinson *et al*., 1999). The deactivation pattern should therefore neither be interpreted as being due to our neutral or grey condition nor as an artefact but directly related to the stimuli-specific emotion processing. Most methodological limitations relating arousal and attention effects and technical limitations are discussed in our previous reports (Northoff *et al*., 2002, 2004). Despite the facts that (i) the pictures presented were matched for emotional dimensions, (ii) psychological states did not differ between groups and (iii) we eliminated from analysis all fMRI signals related to switches between blocks, arousal and attentional effects could not be excluded entirely. Catatonic patients indeed show alterations in attentional functions (Northoff *et al*., 1998), which, however, cannot entirely account for emotion-related orbitofrontal deregulation. Furthermore, effects of attention and arousal have apparently been 'normalized' by GABAergic potentiation since differences in the Neutral > Grey contrast between groups disappeared after lorazepam administration. Finally, because fMRI measurements covered only the frontal lobe, the relationship between the amygdala and MPFC regarding emotional processes remains unclear.

In conclusion, we show that administration of lorazepam, a first-line treatment for catatonia, leads to a modulation of the BOLD-response in OFC

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during emotional processing. In particular, the signal decreases in catatonic patients were regularized by lorazepam compared to healthy controls. These findings have important implications for our understanding of neurophysiological processes in the origin of catatonic symptoms and further research should focus on other imaging studies relating subjective experience of emotions with activation patterns in cortical and subcortical areas.

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