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Delayed onset of late movement-related cortical potentials and abnormal response to lorazepam in catatonia

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Abstract

Catatonia is a psychomotor syndrome with an inability to execute and terminate movements completely, leading consecutively to akinesia and posturing, which both respond almost immediately to benzodiazepines, i.e. gaba-potentiators like lorazepam. However, pathophysiological mechanisms of cortical motor and gaba-ergic dysfunction remain unclear. We therefore investigated movement-related cortical potentials (MRPs) and movement kinematics during a motor task before and after lorazepam.

Ten akinetic catatonic patients were compared with 10 psychiatric (similar age, sex, medication, and underlying psychiatric disease but without catatonic syndrome) and 20 healthy controls. MRPs from frontal (F), central (C), and parietal (P) sites were recorded to obtain measures of early and late readiness potential and movement potential. Kinematic measures included parameters for amplitude of movements, peak velocity, average duration of movements, elevation angle, and angle velocity. The motor task consisted in self-initiated extension of the right index finger. All catatonic and psychiatric control patients received intravenous lorazepam (1 mg), whereas healthy controls were subjected to a placebo-controlled (10 received lorazepam, 10 received placebo) double-blind study design.

Catatonics showed a significantly delayed onset of late readiness and movement potential in central electrodes (Cz, C3) compared with psychiatric and healthy controls. This delayed onset correlated significantly with catatonic motor symptoms and movement duration. Lorazepam led to significantly stronger delays in onset of late readiness potential in left fronto-parietal (F3, C3, P3) electrodes in catatonic patients than in psychiatric and healthy controls.

It is concluded that delayed latencies in late MRP components in catatonic patients may reflect their inability to execute and terminate movements completely. Differential and stronger response to lorazepam in catatonia suggests dysfunction in inhibitory control of cortical motor function with increased gaba-ergic sensitivity.

Keywords: Catatonia; GABA; Kinematics; Lorazepam; Movement potentials

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1. Introduction

Catatonia is a psychomotor syndrome that can be characterized by motor symptoms such as akinesia and posturing (Kahlbaum, 1878; Lohr and Wisniewski, 1987; Taylor, 1990; Fink et al., 1993; Northoff, 1997). Though catatonic patients are able to initiate movements, they are unable to execute fully and terminate the once initialized movement consecutively, leading to posturing and akinesia (Lohr and Wisniewski, 1987; Northoff et al., 1995b). For example, even acute catatonic patients are able to play ball, but they finally remain in a bizarre position holding the limb with the ball against gravity in a particular posture not terminating the movement (Northoff et al., 1995b). In addition, unlike akinesia in Parkinson's disease, catatonic akinesia and posturing can be treated almost immediately with benzodiazepines, like lorazepam, in 60–80% of all acute catatonic patients (Rosebush et al., 1990; Northoff et al., 1995a; Bush et al., 1996). Lorazepam acts as a GABA-A potentiator, therefore suggesting abnormal gabaergic modulation of cortical motor function in catatonia.

Movement-related cortical potentials (MRPs) provide an electrophysiological measure of initiation and execution of voluntary movements (Kornhuber and Deecke, 1964; Deecke et al., 1987; Singh and Knight, 1990). Early and late readiness potential and movement potential are considered as parts of MRPs that are often presumed to be related to distinct cortical motor functions (Deecke et al., 1987; Dick et al., 1987, 1989; Jahanshahi et al., 1995; Deecke, 1996). The early readiness potential, i.e. the early MRP, may reflect the initiation of movements and function of the supplementary motor area (SMA), whereas the late readiness and movement potential, i.e. the late MRPs, may rather be associated with execution and termination of movements and function of motor cortex. Reductions of early MRPs have been reported in Parkinson's disease as probably accounting for their deficit in the initiation of movements (Dick et al., 1987, 1989). Schizophrenic patients showed reductions in early MRPs as well, which, however, may be related with the influence of neuroleptics suppressing dopaminergic function in a similar way as in Parkinson's disease (Singh et al., 1992; Karaman et al., 1997).

In catatonia, however, to our knowledge, no investigations of MRPs have yet been reported. We therefore investigated MRPs and movement kinematics in postacute catatonic patients comparing them with non-catatonic neuroleptically matched psychiatric patients and healthy controls. Since some schizophrenic and affective psychotic patients may be characterized by a so-called 'psychomotor vulnerability' (Taylor, 1990; Northoff, 1997; Northoff et al., 1998), as a predisposition for the development of catatonic syndrome the cortical motor function may be altered even in the postacute state reflecting trait-markers. We therefore hypothesized that, owing to their inability to execute and terminate movements completely, postacute catatonic patients may show alterations only in late and not in early MRPs. In addition, owing to the dramatic therapeutic effects of benzodiazepines, we investigated MRPs before and after lorazepam in all three groups assuming a differential modulation of MRPs by lorazepam.

2. Patients and methods

2.1. Subjects

2.1.1. Catatonic patients

We investigated 10 catatonic patients (six women, four men; age: 41.6 ± 5.3 years; means $\pm$ SD) (see Table 1 for further details). They were selected from all incoming patients at the psychiatric university clinic in Magdeburg and psychiatric clinics in Haldensleben and Blankenburg between July 1996 and January 1998 (incidence, calculated in relation to all admitted systematically screened patients: 2.6%). On admission, six patients were neuroleptically naive (i.e. they never received any neuroleptics), three were neuroleptically untreated (i.e. no neuroleptics in the last 6 months; treatment before with haloperidol (dose range: 5–20 mg) for an average duration of 1.1 ± 0.4 years) and one received clozapine 3×100 mg. No significant differences in psychopathological, kinematic, and MRP measurements

Table 1
Demographic and clinical data in catatonic and psychiatric control patients

Demographic variables	Catatonics ($n=10$)	Psychiatric controls ($n=10$)
Age	41.6 (5.3)	40.8 (4.9)
Years of education	9.5 (1.6)	9.9 (1.8)
Duration of illness (years)	7.5 (5.5)	7.7 (5.9)
Number of hospitalizations	3.3 (2.1)	3.1 (1.9)
Age of onset	34.1 (12.6)	33.5 (8.4)
Time since actual onset (weeks)	5.6 (1.8)	5.5 (1.4)
Duration of treatment (years)	5.1 (4.2)	5.9 (3.9)
Neuroleptics (CPZ) (mg)	180.2 (177.5)	167.0 (153.2)
Anticholinergics (*n* of treated pat.)	7	7
Global Assessment Scale (GAS)	14.9 (3.4)	20.9 (2.1)
Positive and Negative Symptom Scale (PANSS)	85.7 (28.9)	83.1 (31.2)
Hamilton Anxiety Scale (HAM-A)	20.9 (3.4)	20.1 (2.2)
Hamilton Depression Scale (HAM-D)	15.9 (5.9)	19.9 (3.9)
Number of catatonic episodes	3.4 (1.9)	–
Days of catatonic symptoms	14.6 (6.6)	–
Northoff Catatonia Scale (NCS) mean (SD), day 0/1		
NCS (motor)	21.3 (3.2)/1.8 (0.4)	
NCS (affective)	22.9 (2.5)/3.5 (0.9)	–
NCS (behavioral)	20.5 (8.9)/2.9 (0.6)	
NCS (total)	64.7 (12.1)/8.2 (1.9)	
Bush–Francis Scale (BFCRS) [mean (SD), day 0/1]	26.8 (5.7)	3.2 (0.8)
Diagnosis (DSM IV)	295.20 ($n=3$)	295.30 ($n=3$)
	296.54c ($n=7$)	296.54 ($n=7$)

were found between neuroleptically medicated and unmedicated catatonic patients. In addition, three patients took antidepressants (amitriptyline 50–200 mg), two patients received lithium (serum concentration: 0.9 mmol/l) and one received carbamazepin (serum concentration 8 μg/ml). Any patient that had taken benzodiazepines in the 6 months prior to admission [measurement of serum concentration of lorazepam on day 0 according to the method by Greenblatt et al. (1978)] was excluded from the study ($n=3$). Patients with chronic neurological and/or other physical illness, alcohol and/or substance abuses, hyperkinesias and/or dyskinesias as assessed by AIMS (>2; Guy, 1976), and/or neuroleptic-induced hypokinesias as assessed by SEPS (>3; Simpson and Angus, 1970) were excluded from the study.

Co-morbid diagnoses were made according to DSM IV (APA, 1994) on discharge by two independent psychiatrists with a structured clinical interview. All patients were right-handed according to the Edinburgh Inventory of Handedness (Oldfield, 1971). Psychopathological assessments were made with the Global Assessment Scale (GAS; Endicott et al., 1976), the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987), the Hamilton Anxiety Scale (HAM-A; Hamilton, 1959), and the Hamilton Depression Scale (HAM-D; Hamilton, 1960) on day 0 (before initial treatment), 1, and 8 (the day of the MRP investigation).

Catatonic syndrome was diagnosed according to criteria by Lohr (Lohr and Wiesniwski, 1987) (three from 11 symptoms), Rosebush (Rosebush et al., 1990) (four from 12 symptoms), the Bush–Francis Catatonia Rating Scale (BFCRS) (Bush et al., 1996), and the Northoff Catatonia Scale (NCS) (Northoff et al., 1999a) with its different subscales (motor, affective, behavioral). These scales use a rather strict definition of catatonia by relying on a cluster of symptoms, as recommended by Gelenberg (1977). Catatonic symptoms had to be manifest on the day of admission in the presence of both examiners (G.N.; P.D.). Furthermore, patients had to show complete akinesia (i.e. no voluntary movements at all) for at least half an

hour in the presence of the examiners. All patients had to be classified as akinetic catatonic [exclusion of hyperkinetic catatonic patients because hypo- and hyper-kinetic catatonia may differ in pathophysiological mechanisms (Northoff et al., 1995a–b, 1998)] according to all three criteria lists with agreement on every symptom by two independent psychiatrists (G.N.; P.D.), who rated the same patients successively within 1 h on day 0 (before initial medication with lorazepam), day 1 (24 h after admission) and day 8 (the day of the MRP investigation).

On admission, all catatonic patients received solely lorazepam on average 3×2.5 mg intravenously in the first 24 h [means: 5.2 ± 1.3 mg; if patients had reacted already to the second dose ($n=7$), no further lorazepam was given]. According to clinical response to lorazepam in the first 24 h, judged by the criteria of Lohr (Lohr and Wiesniwski, 1987) and Rosebush (Rosebush et al., 1990), we distinguished in general between short-term responders ($n=10$) and non-responders ($n=3$), from which only the former and not the latter were included in the study, because catatonic responders and non-responders to lorazepam might show a different underlying pathophysiological mechanism (Northoff et al., 1995a–b, 1998). After full resolution of catatonic syndrome on day 1 lorazepam was taken off completely and patients received either antidepressants ($n=5$) or/and neuroleptics ($n=8$) (see Table 1 for exact details) in the next days until the MRP investigation, which took place on day 8 after admission 1 week after withdrawal of lorazepam. Serum concentration of lorazepam was measured according to the method by Greenblatt et al. (1978) on day 0 and day 8 (the day of the investigation); if any serum concentration of lorazepam could still be measured on day 8, they were excluded from the study ($n=0$).

2.1.2. Control groups

We investigated two control groups: psychiatric and healthy controls. The age- and sex-matched psychiatric control group (age: 40.2 ± 4.9 years; mean $\pm$ SD; all right-handed) included 10 patients with similar diagnosis according to DSM IV, similar illness duration and similar medication as catatonic patients. These patients were diagnosed according to DSM IV with a semistructured interview by an independent psychiatrist and underwent similar psychopathological assessments as catatonic patients (see above). Subsequently, age, sex, diagnosis, illness duration, and medication were matched between the catatonic group and the psychiatric control group so that the only difference between the two groups was the presence or absence of catatonic syndrome. Psychiatric patients with hypo- (SEPS >3) and hyper-kinetic (AIMS >3) neuroleptic-induced side effects, previous catatonic symptoms/episodes, alcohol/substance abuse, benzodiazepine medication in the last 6 months, and/or neurological/physical illness were excluded from the study. All psychiatric control patients received initially a single injection of lorazepam in the same dose as catatonic patients (see above), were treated with similar medication, and were also investigated with MRP in a similar way.

The healthy control groups (age: 40.1 ± 6.2 years; mean $\pm$ SD; all right-handed) included 20 subjects matched for age and sex to the catatonic group. 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.

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 according to the declaration of Helsinki.

2.2. MRPs

Subjects made self-initiated movements on average every 4–5 s. The movements involved a brisk lifting (i.e. extension) and lowering (i.e. flexion) of the right index finger with rest on a fixed surface. All subjects were trained before the MRP recording session. The mean inter-movement interval was examined and compared between control and patient groups. MRP recordings were made before and after intravenous application of either 1 mg lorazepam (10 catatonics, 10 psychiat-

ric controls, 10 healthy controls) or saline as placebo (10 healthy controls) on 1 day only interrupted by a 15 min break. The study design was double-blind concerning the lorazepam/saline injections in the 20 healthy controls.

The subjects sat in a comfortable reclining chair in a quiet, semi-darkened room. The right arm laid on a board with a fixed surface. Subjects had to decide by themselves when to initiate and to execute the right index finger movement. They were pretrained to move their right index finger on average every 4–5 s. Measurements lasted 10–15 min, such that subjects performed about 100–150 movements.

All recordings were done with Neuroscan and Digitimer D 150 amplifiers. The EEG was recorded with non-polarizable Ag–AgCl collodian fixed electrodes. In orientation on the international 10–20 system the electrode positions were placed at P3, Pz, P4 (upper parietal cortex), C3, Cz, C4 (frontal cortex with precentral gyrus including motor cortex), and F3, Fz, F4 (upper precentral prefrontal cortex including SMA). Linked earlobes were used as references for all electrodes. A ground electrode was placed on the left wrist and the electro-oculogram (EOG) was recorded from electrodes placed at the glabella and the outer and inner canthus of both eyes. The EMG was recorded using a belly-tendon recording from the right m. extensor indicis propius with superficial electrodes. Electrode impedances were less than 5 kΩ. The EEG, EOG, and EMG were amplified using a Digitimer D 150 amplifier. EEG and EOG were amplified (50k) and bandpass filtered from 0.01–50 Hz (time constant 5 s). EMG activity was amplified (10k) and filtered from 10–100 Hz. Signals were digitized at a sampling rate of 150 Hz/channel using a CED-1401 general purpose laboratory interface.

For sampling the baseline-corrected EEG data we used the beginning of the rectified and integrated EMG signal as a trigger for back-averaging. The duration of the sampling window was 2500 ms before and 500 ms after the trigger signal. Prior to off-line analysis, trials contaminated by eye blinks (peak to every amplitude of 80 μV), excessive muscle activity (peak to every amplitude of 80 μV), or amplifier blocking were eliminated and the remaining trials were back-averaged using the trigger on a trial-by-trial basis. Sums of at least 40–50 artefact-free trials [average trials (before/after lorazepam) for catatonics (54/40), psychiatric controls (41/45) and healthy controls (53/56)] were obtained for each subject in each condition.

MRPs were labeled in orientation on the method as established and applied by Dick et al. (1987, 1989) and Jahanshahi et al. (1995). Consecutively, two premovement components of the MRPs, i.e. the early (initial portion of premovement negativity) and late (late premovement negativity after change in slope) readiness potential (RP), were measured. To determine the onset of each of the two components, the averaged waveform for each subject on each evaluated electrode (Fz, Cz, Pz, F3, F4, C3, C4, P3, P4) was examined independently and blindly by three scientists. Intrarater reliability showed high intraclass correlation coefficients between 0.91 and 0.98. Strong interrater reliabilities were maintained with Kappa coefficients averaged 0.96 (SD = 0.03) for latencies and amplitudes of MRPs. In total intra- and interrater variabilities were lower than 3.3%, which is lower than one SD (< 0.02) of values from latencies and amplitudes of MRPs.

For each record, the point of onset of the early and late BP components were marked on the record. Using the marked points, the mean latency of the early RP (L1) (change of the slope from baseline) and the late (L2) (point of change in slope) readiness potential in relation to EMG onset as the trigger signal were measured. In addition, maximal amplitudes of the early (A1) and the late (A2) readiness potential were determined. Amplitudes were measured in relation to a 300 ms baseline, which was obtained by averaging the traces between the point of onset of the early RP and the preceding 300 ms. Furthermore, time onset (L3) and amplitude (A3) of maximal post-motion alterations (after EMG onset), i.e. the movement potential (MP), were determined. All measurements were made on the individual records using a computer-assisted cursoring program.

2.3. Behavioral and neurochemical measures

Effects of lorazepam/placebo were monitored psychologically and neurochemically. Psycho-

logically we determined the Covi-Anxiety Scale (Goldberg and Finnerty, 1982) before and after (10, 20, 30, 45 and 60 min postinjectionem) application of lorazepam/placebo. Serum concentrations of lorazepam [according to the method by Greenblatt et al. (1978)], cortisol and growth hormone were measured before and after (10, 20, 30, 45 and 60 min postinjectionem). In order to monitor the effects of lorazepam on CNS specifically, both 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 comparison scores in the Covi-Anxiety scale and serum levels of lorazepam, the cortisol, and growth hormone are given as the percentage of the respective score/level obtained before lorazepam/placebo administration. For data analysis the integrals of the respective values were calculated such that baselines (before lorazepam/placebo) and alterations after lorazepam/placebo (in percentage) could be compared between the different groups.

2.4. Kinematic measures

The finger movements were recorded using an ultrasonic device that continuously calculates the three-dimensional spatial positions of tiny markers attached to moving body parts (CMS 50, Zebris, Isny, Germany). The method is based on the evaluation of the transmission times of ultrasound impulses emitted from the markers and received by three microphones mounted on a stationary frame (size $40 \times 40 \times 5$ cm^3). The frame was placed about 1 m on the right side of the subject. Three markers were used, one above the middle phalange, one above the distal end of the second metacarpal, and one above the distal end of the radius of the right index finger. Spatial coordinates of the two markers were sampled with a frequency of 20 Hz each and a spatial resolution of 0.2 mm. Kinematic parameters were obtained from all movements.

The positional data of the three markers were analyzed interactively using specially designed software ('3 DA'; Marquardt and Mai, 1994). Raw data were smoothed and time derivatives were calculated by means of kernel estimates (cut-off frequency 12 Hz); this provides a non-parametric estimation of regression functions by moving weighted averages. From the marker's spatial coordinates the three-dimensional trajectories, the tangential velocity along the path and the corresponding accelerations were determined. The following kinematic parameters were determined to characterize right index finger movements (see also Fig. 4): the maximal amplitude of movements (calculated as the total distance traveled along the trajectory path) with distance (mm) and time (ms); the peak velocity with velocity (mm/s) and time (ms); the average time of movement duration (ms); the elevation angle with angle (degrees) and time (ms); the angle velocity with velocity (mm/s) and time (ms). For determination of kinematic parameters a total of 25 movements (i.e. from the accepted MRP trials) were selected and averaged. In order to prevent signal noise from entering into the calculation, a local maximum in the velocity profile was only considered as a peak if the difference from the adjacent minimum was $>3\%$ of the peak velocity.

2.5. Statistics

The two patient groups were compared on demographic data (age, age at onset, duration of illness, number of hospitalizations, neuroleptics) and psychopathological scores (GAS, PANSS, HAM-A, HAM-D) using two-tailed independent *t*-tests.

Differences between groups in MRP and kinematic parameters were calculated using the Kruskal–Wallis Test with one between-subject factor (group) and one within-subject factor (electrode) applying the Mann–Whitney *U*-Test for post hoc comparisons. In addition, we performed multivariate analysis of variance (MANOVA) with four factors concerning groups (catatonics, psychiatric controls, healthy controls), side of electrodes (left, midline), region (frontal, central, parietal), and treatment response (before and after lorazepam).

In addition to the Kruskal–Wallis tests, Mann Whitney *U*-tests, and MANOVA for MRP and kinematic parameters between groups (respectively for before and after lorazepam/placebo), we also

calculated Wilcoxon Tests for differences before and after lorazepam/placebo within groups.

Spearman Rank correlation analyses (using Bonferroni correction for multiple comparisons) were performed between clinical/psychopathological data, MRP latencies and amplitudes, and kinematic parameters for each group separately. Partial correlations using Bonferroni correction were performed to control for effects of age, illness duration, and neuroleptics on those tests for which correlations were significant ($p<0.05$ after Bonferroni correction). Partial correlations were considered significant at $p<0.05$ (two-tailed). In order to reduce the number of variables, following the recommendations of Curtin and Schulz (1998) we correlated only those MRP and kinematic variables with clinical data that showed significant differences between groups. Only those relationships that correlated significantly in both kinds of correlation analysis (Spearman, Partial correlation) were considered as relevant and mentioned in Section 3.

3. Results

3.1. Clinical and demographic data

Demographic data showed no significant differences between catatonics, psychiatric controls, and healthy controls. Subsequently age, age at onset, duration of illness and treatment, number of psychiatric hospitalizations, and neuroleptic dosage (in chlorpromazin equivalents) did not differ significantly between catatonic and non-catatonic psychiatric control patients (see Table 1). Psychopathological scores of HAM-A, HAM-D, and PANSS did not differ significantly between both groups (see Table 1). Only in Global Assessment Scale (GAS; see Table 1) did catatonics show significantly lower ($p<0.001$) scores than psychiatric controls, indicating a poorer global state in catatonia (which is probably due to catatonic symptoms like akinesia and mutism).

3.2. Behavioral and neurochemical measures

Integrals of the respective values for cortisol, growth hormone, serum lorazepam, and anxiety (Covi-Anxiety Scale) before and after lorazepam/placebo are shown in percentage for the four groups in Fig. 1. As predicted (see Hommer et al., 1986), lorazepam induced a decrease in cortisol, an increase in human growth hormone, and a measurable concentration of serum lorazepam in all three groups receiving lorazepam (see Fig. 1). No significant differences in all three measures (cortisol, human growth hormone, serum lorazepam) between the three groups receiving lorazepam were obtained in statistical analysis.

Lorazepam induced marked anxiolysis and sedation in both psychiatric and healthy controls (see Fig. 1 for Covi-Anxiety Scale), whereas in almost all catatonic patients (one exception) it rather led to increased excitation patients showing more inner agitation and higher excitability (see Fig. 1 for opposing curvatures between psychiatric/healthy controls and catatonics).

Inter-movement intervals neither differed significantly between groups before lorazepam (catatonics: 6.5 ± 1.9 s; psychiatric controls: 5.4 ± 1.8 s; healthy controls: 4.9 ± 1.6) nor within groups before and after lorazepam (catatonics: 5.9 ± 1.5 s; psychiatric controls: 6.0 ± 1.7 s; healthy controls: 5.9 ± 1.8 s).

3.3. MRPs

3.3.1. Before lorazepam

First, we compared the two healthy control groups before lorazepam. Both showed no significant differences at all; so, we put them together into one group to raise the number ($n=20$) for statistical comparisons with catatonics ($n=10$) and psychiatric controls ($n=10$).

Second, we compared catatonics with psychiatric and healthy controls. Latency of late onset (L2) of readiness potential in Fz, Cz, and Pz was significantly later in catatonics than in healthy controls (see Table 2 and Fig. 2). Though not reaching a level of statistical significance (probably due to high standard deviations) catatonics also showed later latencies in onset of late readiness potential in Fz, Cz, and Pz than psychiatric controls, which especially in Fz and Cz showed almost similar values as in healthy controls (see Table 2).

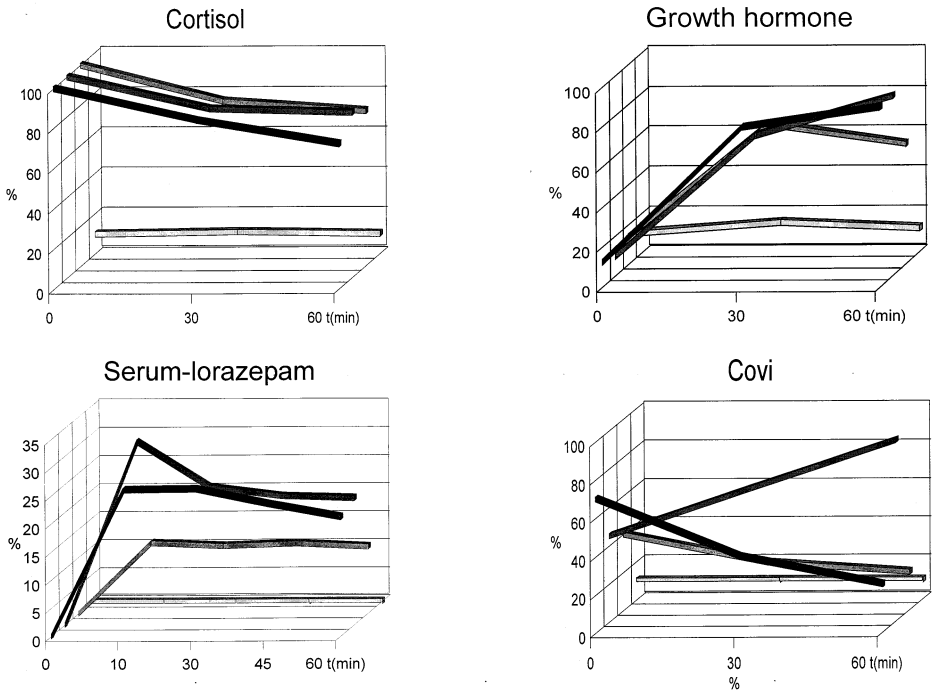

Fig. 1. Effects of lorazepam on psychological and hormonal measures in catatonic patients, and psychiatric and healthy controls. *T* (min) is the time after intravenous administration of lorazepam/placebo; % is the percentage of the respective score/level obtained before lorazepam/placebo administration; Covi is the Covi Anxiety scale. Light gray: healthy controls receiving placebo; gray: healthy controls receiving lorazepam; dark gray: catatonics receiving lorazepam; black: psychiatric controls receiving lorazepam. Note the differences in the influence of lorazepam on Covi Anxiety scale between psychiatric/healthy controls on the one side and catatonic patients on the other; the former show sedation, whereas the latter were rather characterized by increased agitation and excitability.

Table 2
MRPs in catatonics, psychiatric and healthy controls before lorazepam

Electrodes	Latencies[a]	Catatonics ($n=10$)	Psychiatric controls ($n=10$)	Healthy controls ($n=20$)	Variance analysis ($p<0.05$)
Fz	L2	$-462.50\pm123.5^{b,c}$	-588.5 ± 217.0	-612.7 ± 205.8	0.022
	L3	$277.80\pm107.5^{b,c}$	215.8 ± 98.50	208.4 ± 97.0	0.014
Cz	L2	$-453.60\pm188.5^{b,c}$	-570.8 ± 230.4	-612.8 ± 198.7	0.049
	L3	$232.50\pm101.6^{b,c}$	238.5 ± 114.0	185.4 ± 84.70	0.007
Pz	L2	$-410.50\pm138.3^{b,c}$	-467.5 ± 230.8	-581.7 ± 212.0	0.011
	L3	236.70 ± 126.5	175.4 ± 105.6	200.4 ± 98.3	–
F3	L2	-501.80 ± 220.7	-649.8 ± 259.0	-540.8 ± 225.9	–
	L3	204.70 ± 118.0	168.7 ± 99.0	215.0 ± 98.7	–
C3	L2	-501.60 ± 221.8	-610.5 ± 303.50	-521.4 ± 250.0	–
	L3	$280.00\pm118.8^{b,c,d}$	173.5 ± 74.80	185.0 ± 959	0.018
P3	L2	-467.50 ± 191.5	-483.0 ± 260.9	-572.8 ± 135.3	–
	L3	219.50 ± 122.3	226.4 ± 108.7	202.2 ± 90.7	–

[a] L2: onset of late readiness potential (ms); L3: onset of movement potential (ms).
[b] Catatonics versus psychiatric controls.
[c] Post hoc *t*-tests ($p<0.005$).
[d] Catatonics versus healthy controls.

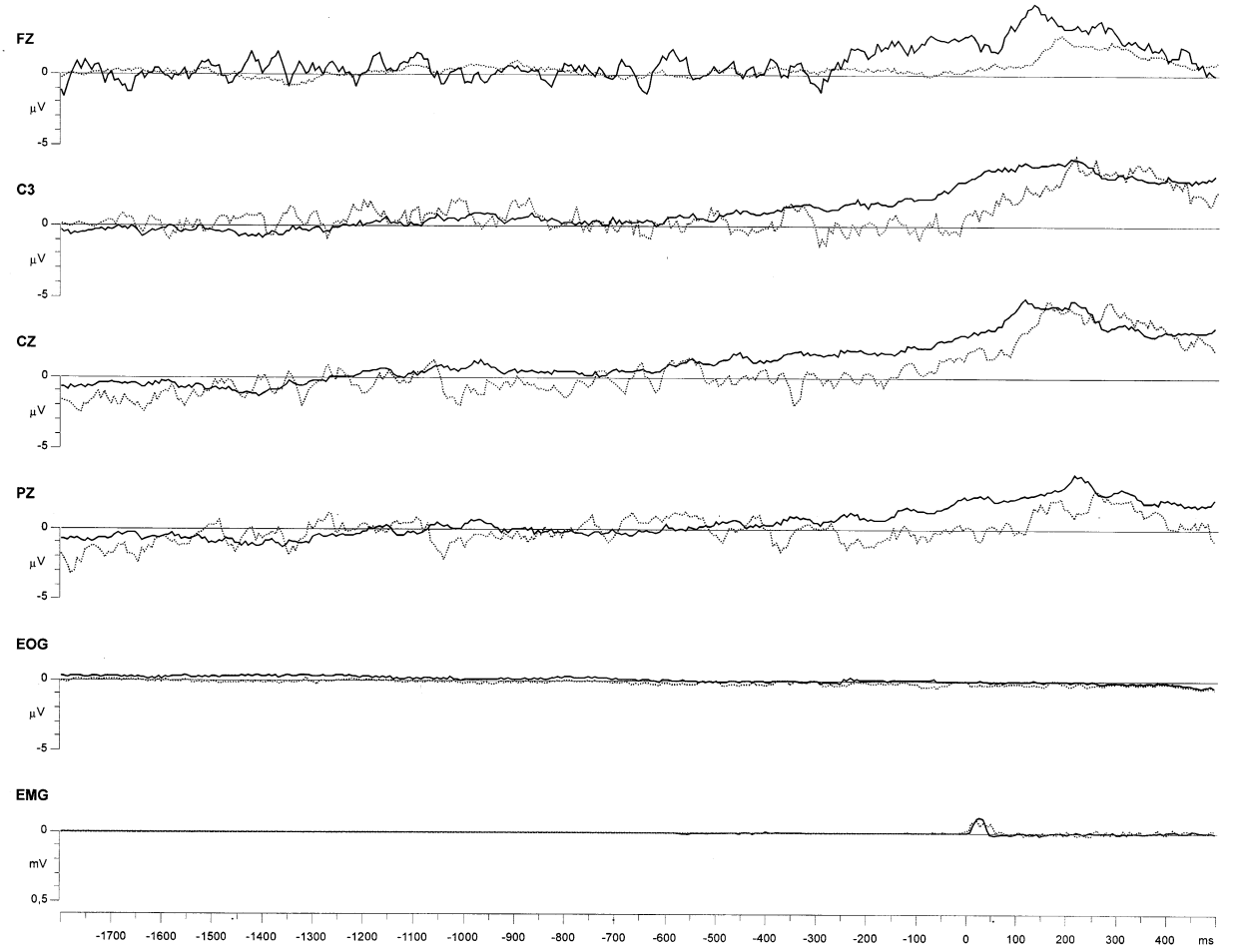

Fig. 2. Grand averages of MRPs in catatonic patients and healthy controls before lorazepam. Thick lines: healthy controls; dotted lines: catatonic patients; EOG: electro-oculogram; EMG: electromyogram. Note the delayed onset of late readiness and movement potentials in catatonic patients compared with healthy controls.

Hence catatonic patients differ in L2 from both control groups, whereas no major differences can be found between psychiatric and healthy controls.

Third, latency of movement potential (L3) in Fz, Cz, and C3 was significantly later in catatonics than in psychiatric (C3) and healthy (Fz, Cz, C3) controls (see Table 2 and Fig. 2). Though not always reaching the level of statistical significance catatonic patients showed delayed L3 in C3 and Fz compared with both control groups, whereas no major differences could be found between psychiatric and healthy controls.

Fourth, in contrast to latencies, we found no differences in amplitudes between catatonic patients and psychiatric controls. However, both psychiatric groups showed lower amplitudes than healthy controls, which, however, did not reach the level of significance.

Fifth, MANOVA demonstrated significant (or almost significant) effects in latency of late readiness potential (L2) for group ($F=6.342$; df $=3.00$; $p=0.001$), region ($F=4.056$; df $=4.00$; $p=0.059$) and region by group (region $\times$ group) interaction ($F=2.367$; df $=8.00$; $p=0.049$), as well as a significant effect for group ($F=5.662$; df $=3.00$; $p=0.012$) and region ($F=4.654$; df $=4.00$; $p=0.029$)

in latency of movement potential (L5). In addition, MANOVA showed significant effects for side ($F=6.334$; df = 2.00; $p=0.002$), region ($F=6.396$; df = 3.00; $p=0.001$), and region by group (region × group) interaction ($F=2.022$; df = 8.00; $p=0.049$) in amplitude of late readiness potential (A2). Subsequently, findings in MANOVA further underline alterations in late MRP components (late readiness potential, movement potential) in catatonia.

In summary, catatonics showed alterations in late MRP components with a significantly delayed onset in late readiness (L2) and movement potential (L3) in fronto-parietal midline (Fz, Cz, Pz) and left lateral central electrodes (C3) compared with psychiatric and healthy controls.

3.3.2. After lorazepam

First, we compared both healthy control groups demonstrating the effects of lorazepam versus placebo. We did not find any significant differences in latencies and amplitudes of MRPs between the healthy placebo ($n=10$) and the healthy lorazepam ($n=10$) group.

Second, we calculated differences in MRPs between catatonics ($n=10$), psychiatric controls ($n=10$), and healthy controls ($n=10$) all receiving lorazepam. Latency of late readiness potential (L2) in C3, as well as latencies of movement potential (L3) in Cz and P3, differed significantly between catatonics and psychiatric controls (see Table 3 and Fig. 3), catatonics showing a later onset in C3L2 and an earlier onset in CzL3/P3L3. Onset of late readiness potential (L2) in Fz, Cz, Pz, F3, C3, and P3 differed significantly between catatonics and healthy controls (and, though not statistically significant, psychiatric controls) showing a later onset in catatonics (see Table 3 and Fig. 3). Latencies of late readiness potential in Cz and F3 differed significantly between psychiatric and healthy controls, showing an earlier onset in healthy controls (see Table 3). In contrast to latencies, we found no significant differences in amplitudes between groups.

MANOVA demonstrated significant effects for region in latency of movement potential (L3; $F=4.691$; df = 4.00; $p=0.049$) and amplitude of late readiness potential (A2; $F=5.002$; df = 4.00; $p=0.001$).

In summary, lorazepam did not lead to significant differences in MRPs in healthy controls compared with those receiving placebo. After lorazepam, catatonics showed a significantly later onset in late readiness potential and a significantly earlier onset in movement potential in medial (Fz, Cz, Pz) and left (F3, C3, P3) fronto-parietal electrodes than psychiatric and healthy controls.

3.3.3. Comparison of MRPs before and after lorazepam

First, a comparison of MRPs latencies and amplitudes before and after lorazepam within groups (Wilcoxon Test) did not show significant differences either in healthy or in psychiatric controls. Catatonic patients showed significant differences in latencies of late readiness potential (L2) in left frontal, central, and parietal electrodes (F3, C3, P3), with later latencies after lorazepam than before (see Table 3 and Fig. 3).

Second, lorazepam led to a slight non-significant delay in L2 in both psychiatric (except in Cz and Pz) and healthy (except in F3) control groups, whereas in catatonic patients this delay in L2 was much stronger, reaching a level of statistical significance in left fronto-parietal (F3, C3, p3) electrodes (see Tables 2 and 3).

Third, latency of movement potential (L3) in fronto-central electrodes was shortened by lorazepam more stronglyr in catatonic patients than in healthy controls, whereas it was rather delayed in psychiatric controls (see Tables 2 and 3).

Fourth, MANOVA demonstrated significant effects for treatment (before/after lorazepam) and region in latency ($F=4.677$; df = 4.00; $p=0.070$) and amplitude ($F=5.997$; df = 4.00; $p=0,.01$) of late readiness and movement potential (L2, A2, L3, A3).

In summary, lorazepam led to a significantly stronger delay in the onset of late readiness potential, as well as to an earlier onset in movement potential in left fronto-parietal (F3, C3, P3) electrodes, in catatonic patients than in psychiatric and healthy controls.

Table 3
MRPs in catatonics, psychiatric and healthy controls after lorazepam

Electrodes	Latencies[a]	Catatonics ($n=10$)	W[b]	Psychiatric controls ($n=10$)	W[b]	Healthy controls ($n=20$)	W[b]	Variance analysis ($p<0.05$)
Fz	L2	$-332.5\pm116.5^{c,d}$	–	-540.5 ± 184.6	–	-580.8 ± 220.9	–	0.048
	L3	168.5 ± 76.5	–	157.8 ± 97.8	–	186.4 ± 98.5	–	–
Cz	L2	$-355.5\pm150.5^{c,d}$	–	$-620.5\pm244.6^{c,f}$	–	-550.8 ± 220.4	–	0.024
	L3	$161.8\pm127.0^{c,e}$	–	267.8 ± 37.5	–	154.8 ± 79.9	–	0.004
Pz	L2	-384.5 ± 86.7	–	-537.8 ± 198.5	–	-500.7 ± 175.8	–	0.015
	L3	199.5 ± 85.7	–	214.0 ± 120.7	–	259.7 ± 147.6	–	–
F3	L2	$-358.4\pm142.9^{c,d}$	0.0284	$-455.8\pm176.7^{c,f}$	–	-560.8 ± 190.1	–	0.018
	L3	191.8 ± 114.7	–	220.8 ± 70.4	–	162.8 ± 72.9	–	–
C3	L2	$-322.0\pm118.4^{c,d,e}$	0.0173	-553.8 ± 316.7	–	-457.0 ± 149.7	–	0.013
	L3	170.0 ± 132.4	–	$265.8\pm79.7^{c,f}$	–	144.8 ± 100.9	–	0.022
P3	L2	$-380.9\pm1\ 99.7^{c,d}$	0.0209	-474.7 ± 212.0	–	-571.5 ± 227.7	–	0.025
	L3	$152.0\pm133.1^{c,e}$	–	283.6 ± 60.4	–	222.8 ± 128.2	–	0.014

[a] L2: onset of late readiness potential (ms); L3: onset of movement potential (ms).
[b] Wilcoxon Test for comparison of MRPs before and after lorazepam.
[c] Post hoc *t*-tests ($p<0.005$).
[d] Catatonics versus healthy controls.
[e] Catatonics versus psychiatric controls.
[f] Psychiatric controls versus healthy controls.

3.4. Movement kinematics

Kinematic parameters of movements before lorazepam showed the following characteristics. Catatonics showed a significantly longer time in average movement duration than healthy controls, but were significantly shorter than psychiatric controls (see Table 4 and Fig. 4). The time for maximal amplitude differed significantly between catatonics and psychiatric controls, the former being shorter than the latter (see Table 4). In addition, psychiatric controls showed in almost all time parameters (time for maximum amplitudes, time for peak velocity, total time, time for maximum elevation angle) significant longer durations than healthy controls and catatonics (see Table 4). In general, duration was longest in psychiatric controls and shortest in healthy controls; catatonics took an intermediate position (see Table 4). No significant differences between groups were obtained in other kinematic measures (see Table 4).

After lorazepam the relations between the three groups concerning time parameters remained more or less the same (see Table 4). Wilcoxon analysis of kinematic parameters before and after lorazepam within groups revealed no significant differences.

In summary, time parameters in kinematic measures differed significantly between groups, showing the longest duration in psychiatric controls and the shortest in healthy controls. Lorazepam had no significant influence on kinematic measures in all three groups.

3.5. Comparison of nosological groups

Psychiatric groups were first classified syndromatically according to the presence/absence of catatonic syndrome into catatonic and non-catatonic psychiatric control patients independent of underlying psychiatric disease (though the latter was matched between catatonic and non-catatonic patients). However, psychiatric patients may also be classified according to their underlying psychiatric disease as either schizophrenic or affective psychosis. We therefore compared MRP and kinematic measurements (before and after lorazepam) between affective and schizophrenic patients within the catatonic (seven affective, three schizophrenic), the psychiatric control (seven affective, three

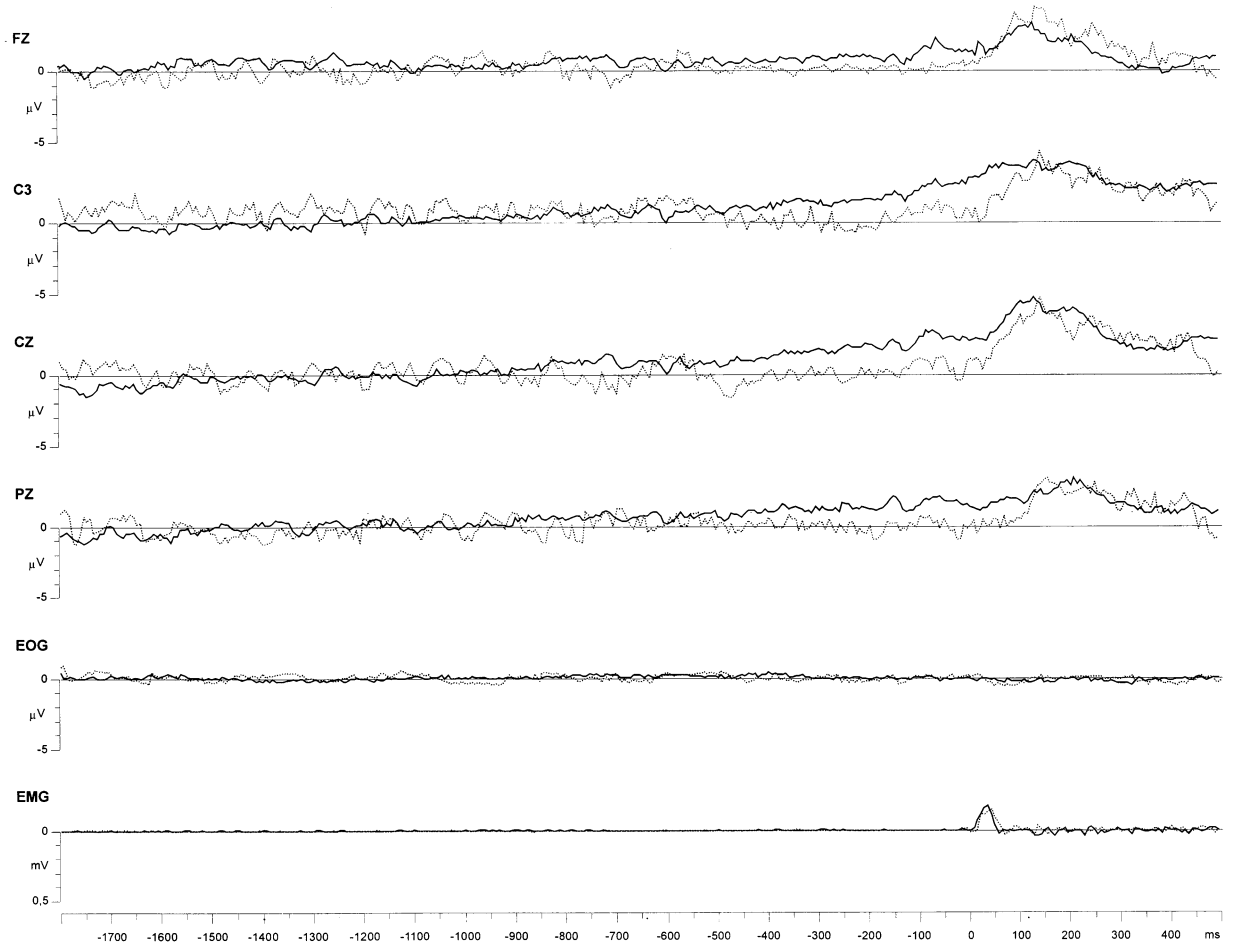

Fig. 3. Grand averages of MRPs in self-initiated movements in catatonic patients and healthy controls after lorazepam. Thick lines: healthy controls; dotted lines: catatonic patients; EOG: electro-oculogram; EMG: electromyogram. Note the delayed onset of the late readiness potential and the earlier onset of the movement potential in catatonic patients after lorazepam compared with catatonic patients before lorazepam (see Fig. 2) and healthy controls after lorazepam.

schizophrenic), and the total psychiatric (catatonics and psychiatric controls; 14 affective, six schizophrenic) sample. Analyses revealed no significant differences in MRPs between affective and schizophrenic patients in all three samples (catatonics, psychiatric controls, catatonics and psychiatric controls). Even those measures in MRP (L2 and L3 in Cz, Fz, Pz, F3, C3, P3) that differed significantly between catatonics and psychiatric controls revealed no significant differences between schizophrenic and affective patients.

In summary, nosological comparisons between affective and schizophrenic patients within psychiatric samples revealed no significant differences, indicating that differences obtained between catatonic and non-catatonic psychiatric patients are rather related with catatonic syndrome itself than with the underlying psychiatric disease.

3.6. Correlation between MRPs and kinematic parameters

Neither in psychiatric nor in healthy controls did we obtain any significant correlation before

Table 4
Kinematic measurements in catatonics and psychiatric and healthy controls before and after lorazepam

	Catatonics ($n=10$)			Psychiatric controls ($n=10$)			Healthy controls ($n=20$)			Variance analysis p	
	Before	After	W[a]	Before	After	W[a]	Before	After	W[a]	Before	After
Maximal amplitude											
distance (mm)	46.23±16.82	45.71±17.23	–	51.02±7.53	45.81±9.21	–	44.80±18.51	44.38±16.41	–	–	–
time (ms)	483.37±143.96[b*]	490.60±138.70	–	643.60±187.15[b*,d**]	634.59±175.38	–	450.65±78.46	479.47±4.52	–	0.0234	0.0201
Peak velocity											
velocity (mm/s)	285.13±117.53	297.14±123.37	–	280.63±94.46	257.90±99.29	–	336.98±177.33	338.69±157.92	–	–	–
time (ms)	206.26±32.23	211.33±46.36	–	271.0±77.9[d*]	251.00±64.48	–	191.91±24.11	211.19±39.52	–	0.055	–
Total time of movement											
duration (ms)	1221.0±357.09[b*,c**]	1178.89±382.13[c*]	–	1520.76±367.05[b*,d**]	1629.25±556.14[d**]	–	823.0±137.89	898.62±123.77	–	0.000	0.0010
Elevation angle											
angle (deg)	42.56±14.55	41.87±12.27	–	39.27±9.60	35.94±11.65	–	38.48±13.20	37.79±10.43	–	–	–
time (ms)	477.44±133.61	483.77±132.64	–	634.7±188.34[d**]	632.25±171.8[d**]	–	440.80±75.53	433.06±94.56	–	0.0228	0.0209
Angle velocity											
velocity (mm/s)	259.0±93.41	268.87±92.44	–	214.5±89.8	268.87±92.45	–	279.63±135.15	283.92±119.42	–	–	–
time (ms)	199.85±25.95	208.22±41.05	–	263.1±73.1	253.0±69.29	–	194.57±27.92	215.46±45.85	–	–	–

[a] Wilcoxon Test for comparison of MRPs before and after lorazepam.
[b] Catatonics versus psychiatric controls.
[c] Catatonics versus healthy controls.
[d] Psychiatric controls versus healthy controls.
* $p<0.05$.
** $p<0.001$.

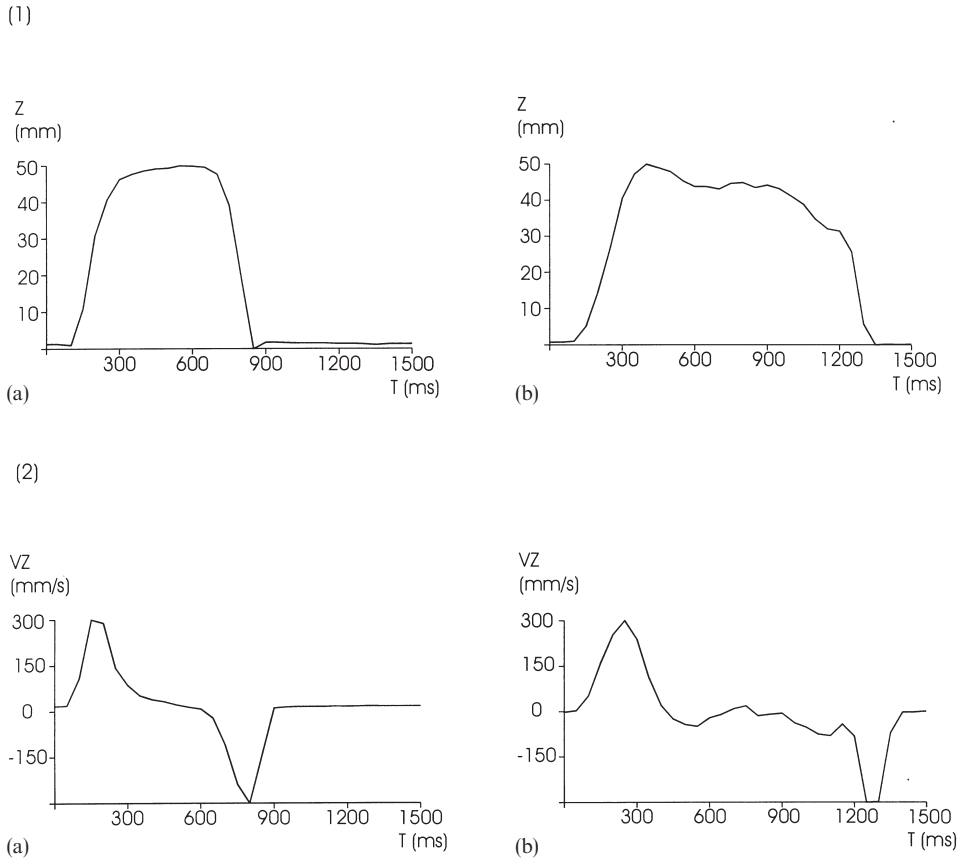

Fig. 4. Kinematic measures before lorazepam: (A) healthy control; (B) catatonic patient; (1) maximal amplitude of movement; (2) velocity of movement; *Z* (mm) amplitude of the movement; *T* (ms) time, i.e. duration of movements; *VZ* (mm/s) velocity of movement. The movement consisted in self-initiated extension and flexion of the right index finger. Note the longer duration of the movement in the catatonic patient, whereas amplitude and velocity showed no differences compared with the healthy control.

lorazepam. In contrast, catatonic patients showed significant correlations of time parameters [time of maximum amplitude (C3, Cz: $r=0.85$; $p=0.004$), average time (C3: $r=0.70$; $p=0.036$), time of maximal elevation angle (Cz: $r=0.867$; $p=0.002$; C3: $r=0.80$; $p=0.001$), angle velocity (Cz: $r=-0.733$; $p=0.025$; C3: $r=-0.80$; $p=0.010$)] with latencies of movement potential (L3) in Cz and C3. No further significant correlations between kinematic parameters and other MRPs measures were obtained in catatonic patients.

After lorazepam, neither healthy nor psychiatric controls showed any significant correlations between kinematic parameters and MRP measures. Catatonic patients showed the following significant correlations after lorazepam. Latency of late readiness potential (L2) in Pz correlated significantly ($r=-0.688$; $p=0.041$) with peak velocity. Latency of movement potential (L3) in Cz correlated significantly with time for peak velocity ($r=0.634$; $p=0.042$) and time for elevation angle ($r=0.695$; $p=0.038$). Latency of movement potential (L3) in C3 correlated significantly ($r=-0.754$; $p=0.019$) with angle velocity.

In summary, kinematic parameters involving time, i.e. temporal duration, correlated significantly with the onset of late readiness potential in Cz and C3 in catatonic patients, whereas neither healthy nor psychiatric controls showed such correlations.

3.7. Correlation with clinical data

Neither catatonics nor psychiatric controls showed any significant correlations between neuroleptic dosage (in chlorpromazin equivalents) and MRPs. No significant correlations were obtained between neurochemical measures of lorazepam (serum lorazepam, cortisol, growth hormone) and MRPs in any of the three groups. In addition, no other demographic data correlated significantly with MRP measures in all three groups.

Catatonic motor symptoms (NCSmot: $r=0.792$; $p=0.011$; NCStot: $r=0.80$; $p=0.01$; duration of catatonic symptoms: $r=0.762$; $p=0.017$) correlated significantly with latency of late readiness potential (L2) in Cz before lorazepam. No further significant correlations between catatonic motor symptoms and other MRP parameters/electrodes (before and after lorazepam) were found.

Affective alterations, as measured with HAM-A and NCSaff, correlated (marginally) significantly with latency of late readiness potential (L2) in Cz (HAM-A: $r=0.821$; $p=0.043$; NCSaff: $r=0.785$; $p=0.054$) before lorazepam, as well as with catatonic symptoms (NCSmot, NCSbeh, NCStot; $r=0.604$-0.682; $p=0.015$-0.023) in catatonic patients.

Psychiatric control patients showed significant correlations between affective symptoms (HAM-A, HAM-D) and latencies of late readiness (L2) and movement (L3) potential in Cz and C3 ($r=-0.672$–0.677; $p=0.025$–0.033) before lorazepam.

Neither in catatonics nor in psychiatric controls were any further significant correlations between clinical data and MRPs after lorazepam obtained. In addition, analyses revealed no significant correlations at all between kinematic (before and after lorazepam) and clinical data.

In summary, correlation analyses showed a relationship between motor symptoms, anxiety, and latency of late readiness potential in medial central electrode (Cz) (before lorazepam) in catatonia.

4. Discussion

The main findings in the present study investigating MRPs in catatonia are as follows. (i) Delayed latencies in late readiness and movement potential in fronto-parietal midline (Fz, Cz, Pz) and left lateral central (C3) electrodes in catatonia. (ii) Significantly stronger effects of lorazepam on latency of late readiness potential in left (F3, C3, P3) and medial (Fz, Cz, Pz) fronto-parietal electrodes in catatonia. (iii) Significant correlations between temporal movement parameters and late latencies in central electrodes (Cz, C3). (iv) Significant correlations between motor symptoms, anxiety, and latency of late central (Cz) readiness potential in catatonia.

The main findings confirm our initial hypothesis of alterations in late MRPs and a differential effect of lorazepam on MRPs as trait markers of cortical motor function in catatonia. To our knowledge the investigation of MRPs in catatonia has not yet been reported, so the discussion will focus on a comparison between catatonia and Parkinson's disease both showing akinesia. Though the present data are clearly of a preliminary nature given the small sample size (see also Section 4.3), results may nevertheless be of interest for the generation of provisional pathophysiological hypothesis.

4.1. Cortical motor function in catatonia

Alterations in MRPs have already been reported in Parkinson's disease (Dick et al., 1987, 1989; Jahanshahi et al., 1995) and schizophrenia (Singh et al., 1992; Karaman et al., 1997; Kubota et al. 1999), with both showing reduction of amplitudes that may be closely related to decrease of nigrostriatal dopamine caused either by the disease itself or by neuroleptics. Though we found a (non-significant) reduction in amplitudes in both psychiatric groups compared with healthy controls, the specific finding with regard to catatonia concerned significantly delayed latencies in late readiness and movement potential. Unlike the reduction of amplitudes, the delay in late MRP latencies can neither be related to underlying psychiatric disease nor to neuroleptic medication since catatonic and psychiatric control patients were matched with regard to underlying psychiatric disease and neuroleptic/psychotropic medication (see Section 2). In addition, nosological comparisons revealed no significant differences in late MRP

latencies between affective and schizophrenic patients, further supporting the assumption of specificity of the present finding with regard to catatonic syndrome.

Differences in MRPs between catatonia (alteration of late latencies) and Parkinson's disease (alteration of early amplitude) may reflect differences in functional mechanisms in the generation of akinesia. Parkinsonian patients are unable to initiate movements by themselves (Jahanshahi et al., 1995), whereas their ability to execute and terminate them completely is still preserved; i.e. they show akinesia without posturing. The deficit in the initiation of movements is thought to be reflected in reduced amplitudes of early MRPs (Dick et al., 1987, 1989; Jahanshahi et al., 1995). In contrast, catatonic patients are still able to initiate movements, as demonstrated in ball experiments (Northoff et al. 1995b), but they can no longer execute and terminate them completely consecutively, leading to posturing with concomitant akinesia (Northoff et al. 1995b; Northoff, 1997). This inability to execute and terminate movements completely may be reflected in delayed latencies of late readiness and movement potential, which would be further supported by the following findings in the present study: (i) significant correlation between onset of late readiness potential in Cz and catatonic motor symptoms; (ii) no alterations in early readiness potential (amplitude, latency) in catatonia which, unlike in Parkinson's disease, may reflect their preserved capacity to initiate movements (Northoff et al. 1995b); (iii) significant correlation between temporal duration of movements (as reflected in kinematic time measures) and latencies of late central (Cz, C3) MRPs only in catatonia but neither in psychiatric nor in healthy controls, suggesting distinct functional organization of generation of movements in catatonia. The lack of correlation between MRPs and kinematic measures in psychiatric and healthy controls may be due to the fact that kinematic parameters are not encoded by a specific group of neurons in one particular anatomical area but rather in various groups of neurons across different anatomical areas with numerous overlappings between distinct kinematic parameters (Fetz, 1992).

Nevertheless, one has to take into account that, owing to investigation of patients in a postacute state, alterations in MRPs do not reflect state markers but trait markers. Hence the inability to execute and terminate movements completely, as suggested by results in late MRPs, may be considered as a trait marker of cortical motor function in postacute catatonic patients. Nevertheless, it cannot be excluded entirely that the capacity to initiate movements, as reflected in early MRPs, may be altered as a state marker in the acute catatonic state as well, whereas, unlike in Parkinson's disease, early MRPs cannot be considered as a trait marker in catatonia.

In addition, functional differences between catatonia and Parkinson's disease are further underlined by consideration of subjective experience of akinesia. Parkinsonian patients are fully aware of their akinetic state and complain about it; catatonic patients, however, are not aware of any movement disturbances, rather suffering from intense and uncontrollable emotions, i.e. anxieties (Northoff et al., 1998). However, additional studies specifically investigating the electrophysiological correlates of termination and posturing of movements would be necessary to specify cortical motor dysfunction in catatonia further.

4.2. Differential response to lorazepam in catatonia

Lorazepam led to significantly stronger delays in latencies of late readiness potential in left (F3, C3, P3) and medial (Fz, Cz, Pz) fronto-parietal electrodes in catatonic patients than in both psychiatric and healthy controls (see Table 3 and Fig. 3). Such a stronger response to lorazepam in catatonia was also observed in latency of movement potential, which was more shortened (though not reaching the level of statistical significance) in catatonics than in psychiatric and healthy controls. This differential response of MRPs to lorazepam suggests an abnormal gaba-ergic control with increased gaba-ergic sensitivity (see below) of cortical motor function in catatonia, which would be further supported by the following clinical observations: (i) immediate therapeutic efficacy of benzodiazepines, like lorazepam, acting as GABA-A potentiators, on akinesia and posturing in catato-

nia (Rosebush et al., 1990; Northoff et al. 1995a–b; Bush et al., 1996); (ii) reversal of therapeutic effects of lorazepam in catatonia by a GABA-A antagonist (Ro 15-1788) with reoccurrence of akinesia and posturing (Wetzel et al., 1987); (iii) therapeutic efficacy of electroconvulsive therapy in akinetic catatonia, which is thought to act via the GABA-system (Northoff, 1997; Petrides et al., 1997).

Exact pathophysiological mechanisms of gaba-ergic cortical motor dysfunction and therapeutic efficacy of lorazepam in catatonia, however, remain unclear, since lorazepam may modulate cortical motor function either directly or indirectly. A direct modulation of cortical motor function would imply that lorazepam acts on GABA-A receptors in primary cortical motor structures like SMA and motor cortex. Such an assumption would be supported by the fact that late MRPs, which in catatonia were particularly modulated by lorazepam, are considered to be closely related to posterior SMA and motor cortex, both involved in execution and termination of movements (Deecke et al., 1987; Jahanshahi et al., 1995; Deecke, 1996). Since lorazepam induced similar but much stronger modulation of MRPs in catatonic patients than in both psychiatric and healthy controls, one may speculatively assume an increased gaba-ergic sensitivity of cortical motor function in catatonia. Such an increased gaba-ergic sensitivity, implying stronger reaction to GABA-A agonists such as lorazepam, may result from decrease of GABA-A receptors in motor cortex, as suggested by a recent SPECT study in postacute catatonic patients (Northoff et al. 1999–c). Since lorazepam reverses catatonic motor symptoms one would have expected a 'normalization' of latencies, which, however could be found only in movement potential but not in late readiness potential. Hence, considering results from late readiness, the potential therapeutic effect of lorazepam on catatonic motor symptoms seems rather paradoxical. One should, however, take into account that we did not investigate acute but only postacute catatonic patients, such that a direct relationship between the effects of lorazepam on motor symptoms and those on MRPs cannot be drawn, which is further supported by the lack of correlation between motor symptoms and MRPs after lorazepam in the present results. The only conclusion that can be drawn is the one that cortical motor function in postacute catatonia seems to be abnormally modulated by gaba-ergic neurotransmission.

The assumption of a central role of abnormal gaba-ergic modulation in execution and termination of movements in catatonia is further supported by animal experiments demonstrating induction and reversal of akinesia/posturing after injection of GABA-A agonists/antagonists into motor cortex (Hikosaka et al., 1985; Kurata and Hoffman, 1994; Kubota, 1996).

In contrast to such a direct effect, it cannot be excluded entirely that lorazepam may modulate cortical motor function rather indirectly via alteration of psychological and prefrontal cortical function, which in turn may influence primary cortical motor structures. Since even postacute catatonic patients showed abnormal psychological reactions to lorazepam compared with psychiatric and healthy controls (see Fig. 1), as well as significant correlations of late central MRPs latencies with motor and affective symptoms, such an indirect effect of lorazepam on cortical motor function should be considered as well. The assumption of such an indirect mechanism may be further supported by subjective experience in catatonic patients, who often report "abnormally intense and uncontrollable emotions leading to a total blockade of movements" (Northoff, 1997; Northoff et al., 1998, 1999a). However, further studies combining emotional–motor stimulation with measurement of GABA-A receptors would be necessary to either verify or falsify the assumption of such an indirect effect of lorazepam on cortical motor function via prefrontal cortical emotional modulation.

4.3. Methodological limitations

First, our results apply only to akinetic catatonia with response to lorazepam, whereas patients with hyperkinesias and/or non-response to lorazepam were excluded (see Section 2). Since pathophysiological mechanisms may differ between hypokinetic and hyperkinetic catatonia, as well as

between responders and non-responders to lorazepam (Northoff et al. 1995a, 1998), exact characterization of the selected patient sample is of major importance. In addition, the present results can only be interpreted as trait markers, whereas they cannot be considered as state markers since catatonic patients were investigated in a postacute state.

Second, correlation data should be interpreted carefully considering the small sample size and the problem of multiple correlations. The sample size is quite small, but one should take into account that catatonia is quite rare nowadays (incidence of 2.6% in relation to all admitted patients; see Section 2). In addition, the problem of multiple correlations should be taken into account. We therefore limited the number variables to be correlated and applied two different kinds of statistical analysis (correlation, partial correlation) for testing relationships; only relations that turned out to be significant in both kinds of analysis were considered as functionally relevant.

Third, the influence of neuroleptic and other psychotropic medication on MRPs remains unclear. Catatonics and psychiatric controls were matched with regard to medication, so that differences between both groups cannot be related to neuroleptics or other psychotropics. In addition, we found no significant correlations between neuroleptic medication (in chlorpromazin equivalents) and MRPs (see Section 2). The exact effects of neuroleptics on MRPs remain unclear (Singh et al., 1992; Karaman et al., 1997). Neuroleptic medication leading to suppression of nigrostriatal dopamine may account for reduction of amplitudes in schizophrenia, as observed in Parkinson's disease (Dick et al., 1989; Jahanshahi et al., 1995). We, too, observed a reduction in amplitudes in neuroleptically medicated patients, i.e. catatonic patients and psychiatric controls, compared with healthy controls; however, this did not reach the level of significance.

The specific finding with regard to catatonia did, however, not concern the amplitudes, but rather the delay in latencies in late MRPs.

Fourth, the effects of lorazepam were investigated in a double-blind placebo-controlled study design only in healthy controls, not in catatonic or psychiatric control patients. Consequently, other factors modulating MRPs in a similar way as lorazepam cannot be excluded entirely in both psychiatric groups. In addition, the measurement of MRPs in Parkinsonian patients would be necessary to compare them directly with those in catatonia.

Acknowledgements

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