

## Right lower prefronto-parietal cortical dysfunction in akinetie catatonia: a combined study of neuropsychology and regional cerebral blood flow

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### ABSTRACT

**Background.** Catatonia is a psychomotor syndrome that can be characterized by behavioural, affective and motor abnormalities. In order to reveal further underlying pathophysiological mechanisms of psychomotor disturbances in catatonia we investigated neuropsychological function and regional cerebral perfusion (r-CBF) in a combined study.

**Methods.** Ten catatonic patients were investigated with Tc-99mECD brain SPECT and compared with 10 psychiatric (similar age, sex, medication and underlying psychiatric diagnosis but without catatonic syndrome) and 20 healthy controls. Neuropsychological measures included tests for general intelligence, attention, executive functions and right parietal visual–spatial abilities. Correlational analyses were performed between neuropsychological measures, catatonic symptoms and r-CBF.

**Results.** Catatonic patients showed a significant decrease of r-CBF in right lower and middle prefrontal and parietal cortex compared with psychiatric and healthy controls as well as significantly poorer performance in visual–spatial abilities associated with right parietal function. Correlational analysis revealed significant correlations between visual–spatial abilities and right parietal r-CBF only in psychiatric and healthy controls but not in catatonic patients. In contrast, attentional measures correlated significantly with motor symptoms, visual–spatial abilities and right parietal r-CBF in catatonia only but not in psychiatric or in healthy controls.

**Conclusion.** Findings are preliminary but suggest right lower prefronto-parietal cortical dysfunction in catatonia, which may be closely related to psychomotor disturbances.

### INTRODUCTION

Catatonia is a psychomotor syndrome that can be characterized by motor symptoms (akinesia, posturing, catalepsy), affective alterations (anxiety, depression, mania) and behavioural anomalies (stereotypies, mutism, stupor, perseveration) (Kahlbaum, 1874; Gelenberg, 1976; Taylor, 1990; Fink *et al.* 1993; Northoff, 1997). However, underlying neuropsychological and pathophysiological mechanisms of psychomotor

disturbances in catatonia remain unclear. As to our knowledge, neuropsychological studies in catatonic patients have not been reported yet, whereas investigations of regional cerebral blood flow (r-CBF) in single catatonic patients found diminished r-CBF in the right parietal cortex (Satoh *et al.* 1993; Liddle, 1994; Galynker *et al.* 1997). A combined investigation of neuropsychological function and r-CBF may further reveal underlying neuropsychological and pathophysiological mechanisms of psychomotor disturbances in catatonia. Relying on results of previous r-CBF studies (Satoh *et al.* 1993; Liddle 1994; Galynker *et al.* 1997) we hypothesized

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that right parietal cortical function may be altered in catatonia, which may be reflected in neuropsychological measures, r-CBF, and altered correlation patterns between both kinds of measures.

Based on these assumptions we included tests for executive (i.e. prefrontal cortical) functions (Trail Making test, Two-Group test, 5-point test), attentional (d2, Colour Word Interference Test), and visual-spatial (i.e. right parietal) abilities (Visual Object and Space Perception Test) in our neuropsychological battery. Using single photon emission tomography (SPECT) r-CBF was investigated. In this preliminary study we investigated 10 akinetic catatonic patients and compared them with 10 psychiatric and 20 healthy controls, correlating neuropsychological measures, regional cerebral blood flow and catatonic symptoms.

## METHOD

### Catatonic patients

We investigated 10 catatonic patients (six women, four men; age,  $41.6 \pm 5.3$  years; for means  $\pm$  s.d.; see Table 1). They were selected from all incoming patients at the psychiatric

university clinic in Magdeburg and psychiatric clinics in Haldensleben and Blankenburg between July 1966 and January 1998 with an incidence, calculated in relation to all incoming patients, of 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  $1.1 \pm 0.4$  years) and one received clozapine  $3 \times 100$  mg. No significant differences in psychopathological measurements and imaging results were found between neuroleptically-naive ( $N = 6$ ) and neuroleptically-untreated/treated ( $N = 4$ ) catatonic patients. In addition, three patients took antidepressants (amitryptilin 50–200 mg), two patients received lithium (serum concentration, 0.9 mmol/l) and one received carbamazepine (serum concentration,  $8 \mu\text{g/ml}$ ). All patients did not take any benzodiazepines in the last 6 months prior to admission, otherwise (measurement of serum concentration of lorazepam on day 0 and day 8 according to the method by Greenblatt *et al.* (1978)) they were excluded from the study ( $N = 3$ ) since benzodiazepines can lead by themselves to alterations

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

Demographic variables	Catatonic patients ( $N = 10$ ) Mean (s.d.)	Psychiatric controls ( $N = 10$ ) Mean (s.d.)
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)
Hospitalizations ( $N$ )	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
GAS	14.9 (3.4)	20.9 (2.1)
PANSS	85.7 (28.9)	83.1 (31.2)
HAM-A	20.9 (3.4)	20.1 (2.2)
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)	—
Rosebush Scale: day 0	10.8 (1.9)	—
day 1	2.4 (1.2)	—
NCS		
Motor	21.3 (3.2)	—
Affective	22.9 (2.5)	—
Behavioural	20.5 (8.9)	—
Total	64.7 (12.1)	—
Diagnosis (DSM-IV)	295.20 ( $N = 3$ )	295.30 ( $N = 3$ )
	296.54c ( $N = 7$ )	296.54 ( $N = 7$ )

GAS, Global Assessment Scale; PANSS, Positive and Negative Symptom Scale; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; NCS, Northoff Catatonia Scale.

in r-CBF (Mathew *et al.* 1995; Wang *et al.* 1996). Patients with chronic neurological or other physical illness, alcohol- and/or substance abuses, hyperkinesias- and/or dyskinesias as assessed by Abnormal Involuntary Movement Scale (AIMS) ( $> 2$ ; Guy, 1976) and/or neuroleptic-induced movement disorders as assessed by the Scale for Extrapyrarnidal Side Effects (SEPS) ( $> 3$ ; Simpson & Angus, 1970) were excluded from the study.

Psychopathological assessments were made with the Global Assessment Scale (GAS) (Endicott *et al.* 1976), the Positive and Negative Symptom Scale (PANS) (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, on day 1 24 h after admission, and on day 8 as the day of SPECT-investigation. All patients were right-handed according to the Edinburgh Inventory of Handedness (Oldfield, 1971). Co-morbid diagnosis was made according to DSM-IV (APA, 1994) on discharge by two independent psychiatrists with a semi-structured clinical interview. Catatonic patients showed the following co-morbid diagnosis according to DSM-IV: catatonic schizophrenia (295.20,  $N = 3$ ), bipolar I disorder (single manic episode) (296.04c,  $N = 1$ ), major depression (multiple episodes) (296.34c,  $N = 1$ ), bipolar I disorder (last episode mania) (296.44c  $N = 2$ ), bipolar I disorder (last episode depression) (296.54c  $N = 3$ ).

Catatonic syndrome was diagnosed according to criteria by Lohr (Lohr & Wiesniewski, 1987) (3 from 11 symptoms), Rosebush (Rosebush *et al.* 1990) (4 from 12 symptoms), the Bush-Francis Catatonia Rating Scale (BFCRS) (Bush *et al.* 1996) and the Northoff-Catatonia Scale (NCS) (Northoff *et al.* 1999a). These scales use a rather strict definition of catatonia by relying on a cluster of symptoms, as recommended by Gelenberg (1976, 1977). Catatonic symptoms had to be manifest on the day of admission for at least 1 h in the presence of both independent examiners (G.N. and P.D.) who rated the patients on day 0 (before initial medication with lorazepam), day 1 (24 h after admission), and day 8 (the day of SPECT investigation). Furthermore, patients had to show complete akinesia with no voluntary movements at all and concomittant posturing i.e. positioning of limbs

against gravity for at least half an hour in the presence of the examiners (see Table 1 for number and scores of catatonic symptoms) so that catatonic patient with hyperkinesias were excluded.

On admission all catatonic patients received only a single doses of intravenous lorazepam (2 mg). According to clinical response to lorazepam in the first 24 h, judged by the above mentioned criteria, we distinguished between short-term responders ( $N = 10$ ) and non-responders ( $N = 3$ ), from which only the former but not the latter were included in the study (Northoff *et al.* 1995a, 1998). After full resolution of catatonic syndrome on day 1 lorazepam was completely withdrawn and patients received either antidepressants ( $N = 5$ ) or/and neuroleptics ( $N = 8$ ) in the next 8 days until SPECT-investigation which took place 1 week after withdrawal of lorazepam. At the time of SPECT investigation patients showed no longer any catatonic symptoms at all whereas symptoms of their underlying disease, as in psychiatric controls, were still present.

#### Control groups

We investigated two control groups, psychiatric and healthy controls. The age- and sex-matched psychiatric control group (age,  $40.8 \pm 4.9$  years; means  $\pm$  s.d.; all right-handed) included patients with similar diagnosis (see above) according to DSM-IV (instead of catatonic schizophrenia we investigated three patients with paranoid schizophrenia (295.30)) and similar medication as catatonic patients but without catatonic syndrome (see Table 1). These patients were diagnosed according to DSM-IV by an independent psychiatrist using a semi-structured interview and underwent similar psychopathological assessment as the 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 psychiatric groups was the presence or absence of akinesia and posturing i.e. of catatonic syndrome. Psychiatric patients with hypokinetic (SEPS  $> 3$ ) and hyperkinetic (AIMS  $> 2$ ) neuroleptic-induced side effects, with catatonic symptoms/episodes on previous hospitalizations, with alcohol/substance abuse, benzodiazepine medication in the last 6 months,

and/or neurological/physical illness were excluded from the study. Initially, they all received a single injection of lorazepam in the same doses as catatonic patients (see above), were treated with similar medications, and were investigated with SPECT also on day 8 after admission.

The healthy control group (age,  $40.1 \pm 6.2$  years; means  $\pm$  S.D.; all right-handed) included 20 healthy 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, and those with 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 and the Administration of Radioactive Substances Advisory Committee. After complete and detailed description of the study to the subjects, written informed consent was obtained.

#### Imaging procedure and data analysis

SPECT was performed with a rotating gamma camera (Siemens, Diacam) with a low-energy, high-resolution collimator (FWHM: 7.5 mm at 10 cm depth). Subjects were positioned supine in a rigid, concave headrest of fixed height with respect to the gantry, and the imaging table was locked into position. These features minimized head movements and facilitated the reproducibility of positioning. Images were obtained at 64 projections in a  $64 \times 64$  matrix acquisition (pixel size: 8 mm) over  $360^\circ$  and 40 s for each projection with a revolution time of 40 min. The acquired frames were corrected for the injected dose and for the individual distribution volume by normalizing to 1.73 m body surface.

SPECT imaging started with measurement of perfusion with 740 Mbq  $^{99m}\text{Tc}$ -ECD, which was given as a slow intravenous injection administered to the subject (eyes closed, 30 min of relaxation before injection) in a dimly lit, quiet room as recommended by Bartenstein *et al.* (1991). Imaging was started 60 min post-injection. To avoid circadian variability (Bartlett *et al.* 1986), the SPECT scans for all subjects were obtained at the same time of day ( $\pm 30$  min).

In addition to SPECT, all subjects underwent magnetic resonance imaging (MRI) on a Siemens

1.5 Tesla system using the standard head coil. Ten contiguous T1 weighted axial images (thickness, 4 mm; gap size, 0.3) were acquired up to planes parallel to the AC-PC line and co-registered with SPECT within the Siemens system mapping and adapting the SPECT images to the outlines and contours of the underlying anatomical MRI. The co-registration of MRI did not only serve for anatomical localization of ROIs but for the exclusion of medium-to-severe atrophy as well, which was recently shown to reduce significantly rCBF and RMRGlu values compared to patients without or with only slight atrophy (Sabri *et al.* 1995). Atrophy was determined in orientation on the method by Sabri *et al.* (1995), two catatonic patients ( $N = 2$ ) were initially excluded so that they did not enter into the study (i.e. they are not included in the initially described group of 10 patients).

Images were reconstructed by filtered back-projection using a Butterworth filter of order 7 and a cut-off frequency of  $0.6 \text{ cm}^{-1}$ . Transverse slices were reorientated to the canthomeatal line using an external line source for landmarking. Slices in the other two orthogonal planes were then reangulated. The spatial resolution was 15 mm (FWHM) in the transaxial plane. Sixty-four axial slices excluding the most basal and the most dorsal slices to minimize partial volume effects, 1.66 mm thick, were reconstructed by using a filter with a cut-off frequency of 0.6 cycles per pixel, and corrected for attenuation with an uniform linear attenuation correction coefficient of  $0.12 \text{ cm}^{-1}$ . Regions of interest (i.e. ROIs) were anatomically determined exactly in reference to co-registered cerebral anatomical MRI using the anatomical atlases of Talairach & Tournoux (1993) and Kretschmann & Weinrich (1991); corresponding ROIs of all slices were summed together and defined in orientation on anatomical MRI as follows: lower medial and lateral prefrontal cortex; lower frontal cortex; upper and lower temporal cortex; middle medial and lateral prefrontal cortex; middle frontal cortex; lower and upper parietal cortex; upper medial and lateral prefrontal cortex; upper frontal cortex; thalami, cerebellum; and, basal ganglia, each on the right and left hemisphere. All ROIs were larger (minimum dimension: 3.75 cm) than  $2.5 \times$  FWHM (15 mm) of our camera to allow a secure quantification (Kojima *et al.* 1989). Average counts per pixel from each

Table 2. Mean *r*-CBF (means  $\pm$  s.d.) in catatonics, and psychiatric and healthy controls

ROI	Hem	Ratio	Catatonics ( <i>N</i> = 10)	Psychiatric controls ( <i>N</i> = 10)	Healthy controls ( <i>N</i> = 20)	<i>P</i> ( <i>V</i> )
Upper frontal	R	O	0.75 $\pm$ 0.04	0.75 $\pm$ 0.03	0.76 $\pm$ 0.04	NS
		W	0.98 $\pm$ 0.06	0.97 $\pm$ 0.04	0.98 $\pm$ 0.05	NS
	L	O	0.74 $\pm$ 0.05	0.74 $\pm$ 0.04	0.75 $\pm$ 0.04	NS
		W	0.99 $\pm$ 0.04	0.98 $\pm$ 0.05	0.99 $\pm$ 0.03	NS
Upper medial prefrontal	R	O	0.73 $\pm$ 0.03 b	0.76 $\pm$ 0.04	0.78 $\pm$ 0.03	0.037
		W	1.01 $\pm$ 0.04	1.01 $\pm$ 0.07	1.04 $\pm$ 0.06	NS
	L	O	0.74 $\pm$ 0.04	0.74 $\pm$ 0.05	0.75 $\pm$ 0.03	NS
		W	0.98 $\pm$ 0.03	0.98 $\pm$ 0.04	0.99 $\pm$ 0.04	NS
Upper lateral prefrontal	R	O	0.72 $\pm$ 0.04 b	0.77 $\pm$ 0.05	0.78 $\pm$ 0.03	0.043
		W	1.02 $\pm$ 0.05	1.03 $\pm$ 0.06	1.05 $\pm$ 0.04	NS
	L	O	0.74 $\pm$ 0.05	0.74 $\pm$ 0.04	0.76 $\pm$ 0.03	NS
		W	1.01 $\pm$ 0.03	1.02 $\pm$ 0.05	1.02 $\pm$ 0.04	NS
Upper parietal	R	O	0.76 $\pm$ 0.04	0.77 $\pm$ 0.05	0.77 $\pm$ 0.03	NS
		W	0.99 $\pm$ 0.04	0.99 $\pm$ 0.06	1.00 $\pm$ 0.04	NS
	L	O	0.74 $\pm$ 0.03	0.75 $\pm$ 0.04	0.75 $\pm$ 0.03	NS
		W	1.01 $\pm$ 0.04	1.02 $\pm$ 0.03	1.02 $\pm$ 0.04	NS
Middle medial prefrontal	R	O	0.65 $\pm$ 0.06 a, b	0.70 $\pm$ 0.05 c	0.75 $\pm$ 0.04	0.015
		W	0.93 $\pm$ 0.06 a, b	1.01 $\pm$ 0.07	1.02 $\pm$ 0.06	0.003
	L	O	0.69 $\pm$ 0.07 b	0.71 $\pm$ 0.04	0.76 $\pm$ 0.03	0.023
		W	0.98 $\pm$ 0.08	1.02 $\pm$ 0.07	1.03 $\pm$ 0.05	NS
Middle lateral prefrontal	R	O	0.69 $\pm$ 0.07 a, b	0.73 $\pm$ 0.05 c	0.77 $\pm$ 0.05	0.027
		W	0.98 $\pm$ 0.06 b	1.00 $\pm$ 0.06	1.02 $\pm$ 0.04	0.049
	L	O	0.72 $\pm$ 0.07 b	0.73 $\pm$ 0.05	0.78 $\pm$ 0.04	0.044
		W	0.98 $\pm$ 0.06	0.99 $\pm$ 0.05	0.99 $\pm$ 0.03	NS
Lower medial prefrontal	R	O	0.68 $\pm$ 0.07 a, b	0.74 $\pm$ 0.06	0.76 $\pm$ 0.04	0.009
		W	0.96 $\pm$ 0.07 a, b	1.05 $\pm$ 0.10	1.04 $\pm$ 0.05	0.015
	L	O	0.71 $\pm$ 0.06 b	0.74 $\pm$ 0.06	0.78 $\pm$ 0.03	0.04
		W	1.01 $\pm$ 0.06	1.05 $\pm$ 0.07	1.06 $\pm$ 0.05	NS
Lower lateral prefrontal	R	O	0.65 $\pm$ 0.06 a, b	0.72 $\pm$ 0.07	0.74 $\pm$ 0.06	0.02
		W	0.93 $\pm$ 0.06 a, b	1.02 $\pm$ 0.09	1.01 $\pm$ 0.08	0.04
	L	O	0.66 $\pm$ 0.06 b	0.72 $\pm$ 0.07	0.75 $\pm$ 0.06	0.002
		W	1.01 $\pm$ 0.05	1.05 $\pm$ 0.07	1.06 $\pm$ 0.05	NS
Lower parietal	R	O	0.64 $\pm$ 0.06 a, b	0.72 $\pm$ 0.06	0.72 $\pm$ 0.05	0.014
		W	0.91 $\pm$ 0.06 a, b	1.02 $\pm$ 0.09	1.00 $\pm$ 0.04	0.008
	L	O	0.66 $\pm$ 0.06 b	0.73 $\pm$ 0.07	0.74 $\pm$ 0.06	0.022
		W	1.01 $\pm$ 0.06	1.01 $\pm$ 0.05	1.02 $\pm$ 0.04	NS

ROI, region of interest; Hem, R/L, right and left hemisphere; O/W, occipital and whole brain ratio; *P* (*V*), variance analysis (ANOVA); NS, non-significant.

a, b, c, *Post hoc t* test (*P* < 0.001).

a, Catatonics < Psychiatric controls.

b, Catatonics < Healthy controls.

c, Psychiatric controls < Healthy controls.

region were used for analysis. Accounting for the problem of inter-individual regional differences within each group, the activity measured in each ROI was divided by the activity obtained in the occipital maximum (i.e. occipital ratio).

Similar to the method applied by Schröder *et al.* (1997), the occipital maximum was obtained by averaging occipital activity from all slices. We used the occipital maximum and not the cerebellum as a reference region because the latter may be altered in catatonia (Joseph *et al.* 1985; Wilcox, 1991) whereas the former remains unchanged by pathophysiological alterations (Northoff, 1997). Values for occipital maxima

revealed neither significant differences (*P* > 0.05) between groups nor higher standard deviations than the other regions of interest. In addition to occipital ratios, we calculated whole-brain ratios, which showed the same findings as occipital ratios (see Table 2). Activities from each ROI were normalized by dividing them through whole-brain activity, which was obtained as averaged counts of all reconstructed slices in the brain showing no significant differences between groups. Neither in occipital maxima nor in whole-brain activity did we find any significant differences between groups.

All images were analysed blindly by two independent raters (C.Z and R.S.). The intra-

observer variability determined for single ROIs in all groups was  $< 3\%$ , which is  $< 1$  s.d. ( $< 0.02$ ) of the ROI values. The inter-observer variability, determined for single ROIs in  $N = 20$  by the two blinded raters, was  $< 4\%$ , which is also  $< 1$  s.d. ( $< 0.04$ ). All ROI values were normally distributed (Shapiro-Wilk's test, Lilliefors's test,  $P > 0.05$ ) so that differences of  $> 2$  s.d. between the three groups were considered abnormal.

### Neuropsychological measures

Standardized, commonly used tests were selected to generate a battery that would assess a number of neuropsychological functions like executive, attentional, and visual-spatial abilities, which are presumed to depend on prefrontal and parietal cortical function.

#### General intellectual function

General intellectual function was measured with the Standard Progressive Matrices (SPM) for the verbally independent age-specific IQ value (Raven, 1976) and the Multiple Vocabulary Test-B (MWT-B) for the verbal age-specific IQ value as an assessment of general pre-morbid intelligence (Lehr, 1995).

#### Attention

Attentional measures included the d2 attention test (Brickenkamp, 1994) with its three measures of percentage of mistakes (F%), concentration performance (CP), and total performance (TP) as well as the Colour-Word Interference Test (CWI) with its three subtests reflecting time for reading (FWL-T), ability of nomination (NOM-T), and ability of interference (SEL-T) (Bäumler, 1985).

#### Visual-spatial abilities

Visual-spatial abilities were assessed with the Visual Object and Space Perception Test (VOSP) with its subtests for recognition of objects (VOSP-object) and silhouettes (VOSP-sil), which are presumed to be specifically associated with right parietal cortical function (Warrington & James, 1991).

#### Executive functions

Executive abilities like sequencing, information processing speed, abstract categorization and ordering (Pantelis *et al.* 1997), are assumed to be

involved in the Trail Making Test (TMT) reflecting the time for connecting numbers (Oswald & Roth 1987), the Two-Group Test according to Kramer with categorization (performance score) of cards (Goldstein & Scheerer, 1941) and the 5-point test with generation of figures (absolute number, perseveration index) between points (Regard, 1991). However, none of these tests reflect executive functions or frontal lobe function exclusively (Pantelis *et al.* 1997).

#### Procedure

The tests were administered in one session two days after the SPECT investigation by a trained psychologist (D.N.) who was blind to the diagnosis. As measured with catatonic scales patients showed no motor anomalies anymore, which may have confounded neuropsychological performance requiring movements. Quality control procedures include double scoring of all test data and periodic review regarding reliability of test administration and scoring. Avoiding early exhaustion and/or monotony and providing alternations between measures with and without time limit the tests were administered in the following order: MWT-B, TMT, SPM, d2, CWI, Two-Group Test, VOSP, 5-point test.

#### Statistical analysis

The two patients 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 (see Table 1).

#### SPECT

Regional differences between groups were calculated using repeated measures analysis of variance (ANOVA) with one between-subjects factor (groups) and one within-subject factor (regions of interest) applying *post hoc t* tests with Bonferroni corrections for multiple comparisons. Statistical analysis of right-left differences were calculated in three different ways. A first global analysis considered right-left differences (i.e. global right-left differences) in a repeated measurement ANOVA with one between-subject factor (group) and two within-subjects factors (regions of interest, level (upper, middle, lower)). In the second step, right-left differences for each region of interest (i.e.

regional right-left differences) were analysed in univariate *t* tests. Finally, all regions of interests of one level were combined in a multivariate analysis for global right-left effects separately for each group and each level. A principal component test (PC-test) was used, which belongs to a class of so-called 'stabilized' multivariate tests designed for tests in small samples of high-dimensional observations (Läuter *et al.* 1996). All calculations were made separately for occipital- and whole-brain ratios respectively. Relations between clinical/psychopathological data and r-CBF in the various regions of interest were calculated using parametric Pearson correlations (see below).

#### Neuropsychology

Neuropsychological test differences between the three groups were tested using analysis of variance with repeated measures and *post hoc t* tests with Bonferroni correction for multiple comparisons. Correlations between demographic, psychopathological and neuropsychological variables were calculated with Pearson Product Moment Correlation analysis (see below). Inter-relationships between a reduced number (only those which differed significantly between catatonic and non-catatonic psychiatric patients; see Results section) of neuropsychological measures were calculated with bivariate Pearson Product Moment Correlation using Bonferroni correction for multiple comparisons.

#### Correlations

Pearson Product Moment Correlation analyses using Bonferroni correction for multiple comparisons were performed between a reduced number of those neuropsychological measures that showed significant deficits or inter-correlations, regional cerebral blood flow and clinical ratings. In addition, we performed partial correlations to control for effects of age, illness duration, and neuroleptics on those tests for which correlations were significant ( $P < 0.05$ ). Partial correlations were considered significant at  $P < 0.05$  (two-tailed). If tests showed significant correlations in both of these analyses they were then investigated by multiple regression analyses. Independent variables were neuropsychological measures as well as potential confounding variables, including age, illness duration and neuroleptics. Dependent

(outcome) variables were indexes of r-CBF in each region of interest. Only those relationships that correlated significantly in all three kinds of analyses (correlation, partial correlation, regression) are mentioned in the Results section.

## RESULTS

### 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 chlorpromazine 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 the Global Assessment Scale (GAS) did catatonics show significantly lower ( $P = 0.001$ ) scores than psychiatric controls (see Table 1) indicating a poorer global state in catatonia, which may be due to catatonic symptoms like akinesia and mutism.

### Regional cerebral blood flow

Catatonic patients showed significantly ( $P < 0.001$ ) lower r-CBF (i.e. occipital- and whole-brain ratio respectively) in the right lower and middle medial and lateral prefrontal cortex as well as in the lower parietal cortex than psychiatric and healthy controls (see Fig. 1 and Table 2). In addition, catatonics showed significantly ( $P < 0.001$ ) lower r-CBF than healthy controls in occipital ratios (and sometimes also in whole-brain ratios) in the following regions (see Table 2): left lower medial and lateral prefrontal cortex; left middle medial and lateral prefrontal cortex; left lower parietal cortex and right upper medial; and, lateral prefrontal cortex. In these regions r-CBF differed significantly only between catatonics and healthy controls whereas no significant differences were found between catatonics and psychiatric controls (see Table 2). No significant differences between groups was found in the upper frontal cortex, upper parietal cortex, cerebellum, occipital maxima, whole brain activity, thalami and basal ganglia. There were no major differences in standard deviations between

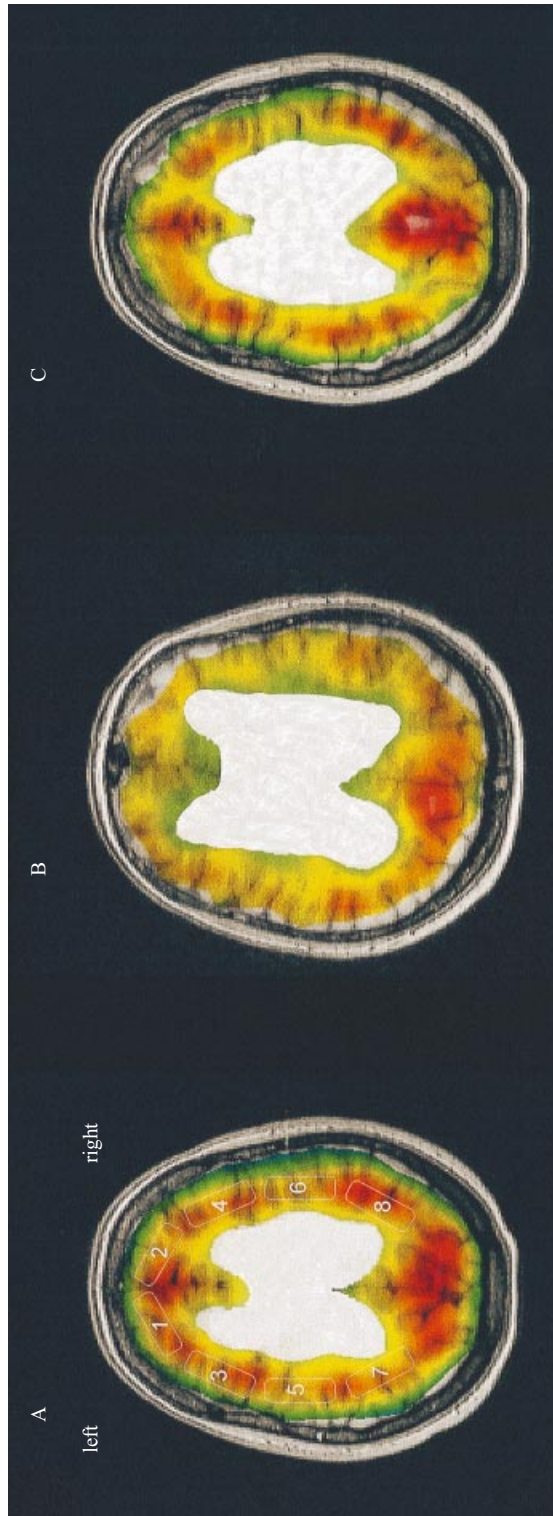


FIG. 1. Regional cerebral blood flow in a healthy control with regions of interest in lower level (A) and corresponding images in a catatonic (B) and psychiatric control (C) patient. Regions of interest: 1, 2, left and right lower medial prefrontal cortex; 3, 4, left and right lower lateral prefrontal cortex; 5, 6, left and right lower prefrontal cortex; and 7, 8, left and right lower parietal cortex.

Table 3. Neuropsychological performances in catatonics and psychiatric and healthy controls

Cognitive function	Neuropsychol. test	Catatonics		Psychiatric controls		Healthy controls		ANOVA			
		Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)	df	F	P	t test
Attention	Test d2										
	TP	302.3	(69.6)	275.4	(69.3)	416.4	(72.3)	35	13.7	0.001	b** c**
	CP	119.2	(33.1)	104.6	(32.2)	166.9	(36.5)	35	11.1	0.000	b** c**
	CWI										
	FWL-T	48.5	(6.7)	45.8	(5.1)	54.9	(6.1)	37	6.4	0.005	b* c**
Visual-spatial abilities	NOM-T	52.6	(11.4)	53.6	(11.2)	54.3	(6.3)	37	0.4	0.648	
	SEL-T	53.4	(10.2)	53.3	(7.2)	51.3	(5.5)	37	0.1	0.946	
	VOSP										
Executive function	Silhouettes	18.6	(5.0)	22.5	(3.6)	22.9	(5.2)	37	1.9	0.174	
	Objects	15.3	(3.6)	17.1	(2.3)	18.3	(1.9)	37	4.6	0.015	a* b*
Executive function	Trail-Making										
	Mean time	111.4	(32.0)	127.5	(49.2)	69.5	(16.8)	38	10.7	0.000	b** c**
	5-Point										
	Total points	25.8	(7.9)	24.7	(7.3)	32.7	(18.1)	37	1.5	0.257	
	Persev.-index	0.2	(0.1)	0.2	(0.2)	0.2	(0.1)	37	1.6	0.218	
Executive function	2 Group										
	Total points	3.1	(1.2)	3.4	(1.3)	4.3	(1.0)	37	4.7	0.013	b** c*

a, Significant group differences between catatonics and psychiatric controls.

b, Significant group differences between catatonics and healthy controls.

c, Significant group differences between psychiatric and healthy controls.

\*  $P \leq 0.05$ ; \*\*  $P \leq 0.01$ .

groups, so that significant differences between groups are rather unlikely to be accounted for by differences in variability.

Global right-left differences were significant in lower level in healthy controls ( $P = 0.004-0.012$ ) and in all levels (upper, middle, lower) in catatonic patients ( $P = 0.001-0.023$ ) whereas there were no significant right-left differences in any of the levels in psychiatric controls. Catatonic patients showed significant ( $P < 0.001$ ) right-left alterations in lower and middle medial and lateral prefrontal cortex as well as in lower parietal cortex whereas in psychiatric controls significant right-left differences were found only in prefrontal but not in parietal cortex. Healthy controls showed significant right-left alterations in neither prefrontal nor in parietal r-CBF. This is further underlined by calculation of right-left differences in multivariate analysis. Significant effects of regions ( $F = 12.44$ ;  $df = 4.00$ ;  $P = 0.001$ ) and groups ( $F = 10.95$ ;  $df = 2.43$ ;  $P = 0.005$ ) were demonstrated. The group-by-region interaction was also significant ( $F = 3.14$ ;  $df = 8.88$ ;  $P = 0.006$ ), indicating different right-left patterns of perfusion between the three groups.

In summary catatonics showed significant lower r-CBF and abnormal right-left pattern in the right lower prefrontal and parietal cortex compared with psychiatric and healthy controls.

### Neuropsychological measures

No significant difference in measures of general intellectual function (SPM, MWT-B) was found between catatonics and psychiatric controls (see Table 3). Measures of attentional functions (i.e. d2-CP/TP, CWI-FWL-T/NOM-T/SEL-T) revealed no significant differences between catatonics and psychiatric controls whereas both psychiatric groups differed significantly from healthy controls (see Table 3). Visual-spatial abilities as measured with VOSPobject differed significantly between catatonic patients and psychiatric and healthy controls, both control groups showing significantly higher scores (better performance) than catatonics (see Table 3). VOSPsilhouettes revealed no significant differences between both psychiatric groups (see Table 3).

Executive functions, investigated with the Two-Group test, the 5-point test and the Trail Making test, showed no significant differences between catatonics and psychiatric controls though both groups differed significantly from healthy controls (see Table 3). In catatonic patients VOSPobject correlated significantly with d2-CP ( $r = 0.864$ ;  $P = 0.003$ ) and d2-TP ( $r = 0.785$ ;  $P = 0.001$ ) as well as with CWI-FWL-T ( $r = 0.659$ ;  $P = 0.019$ ) and CWI-

NOM-T ( $r = 0.598$ ;  $P = 0.047$ ). No significant correlations were found between VOSPobject and other neuropsychological measures in either the psychiatric or the healthy controls.

In summary, catatonic patients differed from psychiatric and healthy controls only in visual-spatial abilities (i.e. VOSPobject) showing significantly lower performance and abnormal inter-correlations with attentional measures (d2, CWI).

#### 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 (see above). However, psychiatric patients may also be classified according to their underlying psychiatric disease as either schizophrenic or affective psychosis. We therefore compared r-CBF and neuropsychological measurements between affective and schizophrenic patients within the catatonic (7 affective, 3 schizophrenic), the psychiatric control (7 affective, 3 schizophrenic) and the total psychiatric (catatonics and psychiatric controls; 14 affective, 6 schizophrenic) sample. Analyses revealed no significant differences in r-CBF and neuropsychological measures between affective and schizophrenic patients in all three samples. Even those measures in r-CBF (right lower prefrontal and parietal cortex) and neuropsychology (visual-spatial abilities), which 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 the differences obtained between catatonic and non-catatonic patients are related to the catatonic syndrome itself rather than to the underlying psychiatric disease. Hence, despite different underlying psychiatric diseases patients with similar behavioural presentations, as reflected in catatonic syndrome, seem to show a certain neurophysiological and neuropsychological uniformity.

#### Correlation with clinical data

Neither catatonics nor psychiatric controls showed any significant correlations between neuroleptic dosage in chlorpromazine equivalents, neuropsychological measures and r-CBF. In addition, no other demographic data correlated significantly with neuropsychological measures and r-CBF in all three groups.

Catatonic motor symptoms as measured with NCSmot and NCStot correlated significantly with d2-TP ( $r = -0.665/0.668$ ;  $P = 0.026/0.031$ ) and right lower parietal r-CBF ( $r = 0.739$ ;  $P = 0.020$ ) in catatonic patients. In addition, catatonic symptoms (NCSmot, NCSbeh, NCStot) correlated significantly with anxiety as measured with HAM-A ( $r = 0.604-0.682$ ;  $P = 0.015-0.023$ ). In catatonics, depressive symptoms (HAM-D) correlated with right lower parietal r-CBF ( $r = -0.716$ ;  $P = 0.015$ ), whereas in psychiatric controls HAM-D correlated significantly with right lower medial ( $r = -0.732$ ;  $P = 0.001$ ) and lateral ( $r = -0.649$ ;  $P = 0.003$ ) prefrontal r-CBF.

Only psychiatric and healthy controls, but not catatonic patients, showed significant negative correlations ( $r = -0.760$  to  $0.769$ ;  $P = 0.008-0.016$ ) between age and r-CBF (occipital and whole-brain ratios) in left lower medial and lateral prefrontal cortex. In summary, correlation analyses revealed a relationship between catatonic symptoms, attentional measures and right lower parietal r-CBF.

#### Neuropsychological measures and r-CBF

No significant correlations between measures of general intellectual function (SPM, MWT-B) and r-CBF were found in any of the three groups. VOSPobject correlated significantly with right ( $r = 0.836$ ;  $P = 0.038$ ) and left ( $r = 0.931$ ;  $P = 0.011$ ) lower lateral prefrontal r-CBF as well as with right lower parietal r-CBF ( $r = 0.836$ ;  $P = 0.038$ ) in psychiatric and healthy controls, whereas catatonics did not show any significant correlations between VOSP and r-CBF (see Table 4). In catatonia, the Trail Making Test correlated significantly with right ( $r = 0.788$ ;  $P = 0.012$ ) and left ( $r = 0.769$ ;  $P = 0.016$ ) upper lateral prefrontal r-CBF (see Table 4). Psychiatric and healthy controls showed significant correlations between TMT and right upper lateral prefrontal ( $r = 0.959$ ;  $P = 0.01$ )

Table 4. Correlations between neuropsychological measures and fronto-parietal regional cerebral blood flow

Test	Group	Lower parietal		Lower lateral frontal				Upper parietal		Upper lateral frontal					
		Left	Right		Left		Right		Left	Right		Left		Right	
			<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>		<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
VOSP	ob	cat	—	—	—	—	—	—	—	—	—	—	—	—	—
		pcont	—	0.836	0.038	0.931	0.011	0.836	0.038	—	—	—	—	—	—
		hcont	—	0.937	0.001	0.899	0.019	0.917	0.012	—	—	—	—	—	—
5-point	tp	cat	—	—	—	—	—	—	—	—	—	—	—	—	—
		pcont	—	—	—	—	—	—	—	—	—	—	—	—	—
		hcont	—	—	—	—	—	—	—	—	—	—	—	—	—
	pi	cat	—	—	—	—	—	—	—	—	—	—	—	—	—
		pcont	—	-0.910	0.012	—	-0.923	0.002	—	—	—	—	—	—	—
		hcont	—	-0.899	0.019	—	-0.879	0.009	—	—	—	—	—	—	—
TMT	cat	—	—	—	—	—	—	—	—	0.769	0.016	0.788	0.012	—	—
	pcont	—	—	—	—	—	—	—	0.913	0.004	—	0.959	0.010	—	—
	hcont	—	—	—	—	—	—	—	0.906	0.008	—	0.939	0.009	—	—

VOSP ob, Visual Object and Space Perception Test. Perception of objects: 5-point Test (tp, total points; pi, perseveration index); TMT, Trail Making Test. cat, Catatonic patients (*N* = 10); pcont, psychiatric controls (*N* = 10); hcont, healthy controls (*N* = 20).

and right upper parietal ( $r = 0.913$ ;  $P = 0.004$ ) r-CBF.

The perseveration index in the 5-point test correlated significantly with right lower parietal r-CBF ( $r = -0.910$ ;  $P = 0.012$ ) and right lower lateral prefrontal r-CBF ( $r = -0.923$ ;  $P = 0.002$ ) in psychiatric and healthy controls whereas in catatonics no significant correlations were found (see Table 4).

In summary, correlation analyses revealed an abnormal correlation pattern of neuropsychological measures (VOSP, TMT, 5-point) with right lower prefronto-parietal r-CBF in catatonia compared with both psychiatric and healthy controls.

## DISCUSSION

The main findings of the present study in akinetic catatonia are as follows: (i) significantly lower r-CBF in right lower prefrontal and parietal cortex in catatonia than in psychiatric and healthy controls; (ii) deficits in visual-spatial abilities in catatonia including altered correlation pattern with right parietal r-CBF; (iii) significant right-left alterations of prefronto-parietal r-CBF in catatonia; (iv) significant correlations of attentional function with motor symptoms and right parietal r-CBF only in catatonia but not in psychiatric or in healthy controls.

Findings of the present study confirm our initial hypothesis of right parietal cortical dysfunction with deficits in right parietal r-CBF and visual-spatial abilities in catatonia. Though the present correlational data are clearly of a preliminary nature, given the small sample size (see also methodological limitations), correlation patterns may, nevertheless, be of interest for the generation of provisional pathophysiological hypothesis.

### Right lower prefronto-parietal cortical dysfunction in catatonia

The main finding in the present study concerns the decrease of r-CBF in right lower prefrontal and parietal cortex, which, in contrast to reductions of r-CBF in left prefrontal cortex, occurred only in catatonia but not in psychiatric controls. Subsequently, reduction of r-CBF in right lower prefronto-parietal cortex seems to be specific for catatonia, which is further supported

by nosological comparisons (see above) and similar r-CBF findings in single catatonic patients (Satoh *et al.* 1993; Liddle, 1994; Galynker *et al.* 1997). In addition, the particular role of the right parietal cortex in catatonia is further underlined by results from neuropsychological measures. Catatonics showed poorer performance in visual-spatial abilities in VOSPobject, a test specifically designed for the differentiation between right and left parietal cortical function showing alterations only in patients with right parietal lesions (Warrington & James 1991). The assumption that right parietal cortical function may be crucial in pathophysiology of psychomotor disturbances in catatonia is further underlined by the following findings in the present study: (i) significant correlations between catatonic motor symptoms and right parietal r-CBF; (ii) altered correlation pattern between VOSPobject and right parietal r-CBF in catatonia compared to psychiatric and healthy controls; and (iii) altered correlation patterns between other neuropsychological measures (Trail Making Test, 5-point) and right parietal r-CBF in catatonia only, and not in psychiatric or in healthy controls.

Consequently, right parietal cortical function may be closely related to catatonic motor symptoms like catalepsy and posturing where patients are unable to terminate movements (Northoff, 1997; Northoff *et al.* 1995b). Similar symptoms have been observed in patients with isolated right parietal cortical lesions (Fukutake *et al.* 1993; Saver *et al.* 1993) thus, further supporting the crucial role of right parietal cortical dysfunction in catatonia. Due to the fact that we investigated only post-acute catatonic patients showing no symptoms at the time of investigation the present finding of right lower prefronto-parietal cortical dysfunction must be considered as a trait marker present in the remitted state and thus predisposing for the manifestation of catatonic syndrome. Since, however, we found correlation of right parietal cortical dysfunction with catatonic motor symptoms, alteration in right parietal cortical function may be likely to occur in the acute catatonic state as well, which is supported by recent findings in acute catatonic patients (Galynker *et al.* 1997; Andrew Francis, personal communication).

The exact neuropsychological and neuro-

physiological mechanisms of such an inability to terminate movements remain, however, unclear. Considering our finding of an altered correlation pattern between attentional measures, motor symptoms, visual-spatial abilities, and right parietal cortical r-CBF (see above) one may assume a specific disturbance in attention-to-movements in catatonia without general attentional deficits. Such an assumption is further supported by investigation of subjective experience (Northoff *et al.* 1998). In contrast to Parkinsonian patients, catatonics are not aware of their movement disturbances while being fully aware of their inner emotional experiences, so that they seem unable to shift their attention from emotions to movements. Neurophysiologically, such an inability to shift attention from emotions to movements may be reflected in right lower prefronto-parietal cortical dysfunction. This was demonstrated in recent studies where the right prefronto-parietal cortex is activated when attention-to-movements is required (Deiber *et al.* 1996; Gitelman *et al.* 1996; Jueptner *et al.* 1997), which is in line with anatomical connectivity showing reciprocal connections between lower prefrontal and parietal cortex (Carmichael & Price, 1995). Hence, patients showing either a decrease, as it seems to be the case in catatonia, or an increase, as it is probably the case in Parkinsonic and schizophrenic patients with delusions of alien control, in attention-to-movements may be characterized by concomitant alterations in prefrontal and parietal cortical areas, which is supported by present results and findings of orbitofrontal dysfunction (Northoff *et al.* 1999b) in catatonia as well as by the respective imaging findings in Parkinson's disease (Samuel *et al.* 1997) and schizophrenia (Spence *et al.* 1997).

#### Methodological limitations

First, correlation data in the present study are clearly of a preliminary nature given the small sample size with 10 catatonic patients. However, considering the fact that catatonia is quite rare (incidence of 2.6% in relation to all incoming patients) as well as the careful definition and selection of the current sample (see Method section) such a small sample size may be at least partially justified.

Secondly, considering the problem of meaningful pathophysiological interpretation of stat-

istical correlations, the small sample size, and the statistical problem of multiple comparisons, individual correlation (as opposed to a general pattern) may not be reliably interpretable, so that analysis of single correlations must necessarily remain speculative.

Thirdly we investigated only akinetic catatonic patients responding well to lorazepam, whereas hyperkinetic catatonics and non-responders to lorazepam were excluded (see Method). This limitation is important to mention since hypokinetic and hyperkinetic catatonia as well as responders and non-responders to lorazepam may probably be characterized by distinct underlying pathophysiological mechanisms (Northoff *et al.* 1995a, 1998). Consequently, the present result of right parietal cortical dysfunction may apply exclusively to patients with akinetic catatonia responding well to lorazepam whereas hyperkinetic catatonics and non-responders should be investigated separately.

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