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Decreased density of GABA-A receptors in the left sensorimotor cortex in akinetic catatonia: investigation of in vivo benzodiazepine receptor binding

Georg Northoff, Reiner Steinke, Christian Czcervenka, Reiner Krause, Sven Ulrich, Peter Danos, Dieter Kropf, HansJürgen Otto, Bernhard Bogerts

Abstract

**Objectives**—Catatonia is a psychomotor syndrome with concomitant akinnesia and anxiety which both respond almost immediately to benzodiazepines such as lorazepam. The benzodiazepine receptor distribution was therefore investigated in akinetic catatonia with single photon emission tomography (SPECT) using iodine-123-iomazenil (\(^{123}\)I Iomazenil).

**Methods**—Ten akinetic catatonic patients, 10 psychiatric controls (similar age, sex, medication, and underlying psychiatric diagnosis but without catatonic syndrome), and 20 healthy controls were investigated with SPECT 2 hours after injection of \(^{123}\)I Iomazenil. To exclude potential effects of cerebral perfusion (r-CBF) r-CBF was additionally investigated with Tc-99mECD SPECT.

**Results**—Catatonic patients showed significantly lower iomazenil binding and altered right-left relations in the left sensorimotor cortex compared with psychiatric (p<0.001) and healthy (p<0.001) controls. In addition, there was significantly lower r-CBF in the right lower prefrontal and parietal cortex in catatonia whereas in the left sensorimotor cortex no differences in r-CBF between groups were found. Catatonic motor and affective symptoms showed significant correlations (p<0.05) with benzodiazepine binding in the left sensorimotor cortex as well as with right parietal r-CBF.

**Conclusions**—Reduced iomazenil binding suggests decreased density of GABA-A receptors in the left sensorimotor cortex in akinetic catatonia. In addition to reduced GABA-A receptor density in the left sensorimotor cortex the parietal cortex seems to be involved in pathophysiology of catatonic symptoms. It is concluded that, considering results from correlation analyses, both emotional and motor symptoms in catatonia seem to be closely related to left sensorimotor and right parietal alterations.

(J Neurol Neurosurg Psychiatry 1999;67:445–450)

Keywords: catatonia; GABA-A receptors; motor cortex; parietal cortex

Catatonia is a psychomotor syndrome which can be characterised by concomitant motor and emotional abnormalities. Patients show complete akinnesia and intense and uncontrollable anxieties. Several clinical studies have shown the therapeutic efficacy of benzodiazepines. Lorazepam, a benzodiazepine, leads to potentiation of inhibition mediated by GABA-A receptors and alterations in density of GABA-A receptors in cortical motor areas may thus be assumed in akinetic catatonia.

The GABA-A receptors have never been studied in akinetic catatonia. We therefore investigated akinetic catatonic patients with single photon emission computed tomography (SPECT) using iodine-123-labelled iomazenil \(^{123}\)Iiomazenil) as a radioligand that selectively binds with high affinity to the benzodiazepine subunit of the GABA-A receptor complex in the human brain. Clinical studies in healthy volunteers have shown that it has a high brain uptake, relatively slow washout of radioactivity, a long half life, and appropriate regional distribution. To exclude effects of cerebral perfusion on iomazenil binding and distribution we additionally investigated regional cerebral blood flow (r-CBF) with Tc-99m ECD in the same subjects immediately after I-123-Iomazenil SPECT.
substance misuse, hyperkinesias, or dyskinesias as assessed with the abnormal involuntary movement scale (AIMS), or neuroleptic induced movement disorders as assessed with the scale for extrapyramidal side effects (SEPS) >3 were excluded from the study.

Psychopathological assessment were made with the global assessment scale (GAS), the positive and negative symptom scale (PANS), the Hamilton anxiety scale (HAM-A), and the Hamilton depression scale (HAM-D) on days 0, 1, and 8. All patients were right handed according to the Edinburgh Inventory of handedness. Comorbid diagnoses were made according to DSM IV on discharge showing the following diagnosis: catatonic schizophrenia (295.20: n=3); bipolar I disorder (296.04c: n=1); major depression (296.44c: n=1); bipolar I disorder (296.44c: n=2); bipolar I disorder (296.54c: n=3).

Catatonic syndrome (number of catatonic episodes during illness: 3.0 (SD 0.8); days of catatonic symptoms during current episode: 14.5 (SD 5.8) days) was diagnosed according to criteria by Lohr and Wisniewski (three from 11 symptoms), Rosebush et al (four from 12 symptoms), the Bush-Francis catatonia rating scale (BFCSR), and the Northoff catatonia scale (NCS). Catatonic symptoms had to be manifest for at least half an hour on the day of admission in the presence of both examiners (GN; PD) who rated the same patients successively within 1 hour on days 0, 1, and 8. Only patients with akinetic (exclusion of hyperkinetic catatonia; see Northoff et al) catatonia and reponse to lorazepam (single intravenous doses of 2 mg) in the first 24 hours were included. In the next days all patients received no benzodiazepines but antidepressant (n=5) or neuroleptic drugs (n=8) until SPECT investigation, which took place on day 8.

CONTROL GROUPS

Two control groups were investigated: (1) an age and sex matched psychiatric control group (age: 40.8 (SD 4.9) years; all right handed) comprised patients with a similar diagnosis, illness duration, exclusion criteria, and medication as catatonic patients but without catatonic syndrome. The medication and SPECT protocols were similar to the catatonic groups. (2) A healthy control group of 20 subjects (age: 40.1 (SD 6.2) years; all right handed) matched for age and sex. Subjects with a history of psychiatric, neurological, or serious physical illness, drug or alcohol misuse, or first degree relatives with major psychiatric or neurological disorders were excluded. Ethics permission was obtained from the ethics committee of the University of Magdeburg and the administration of radioactive substances advisory committee. Informed consent was obtained from all subjects.

IMAGING PROCEDURE AND DATA ANALYSIS

Iomazenil was synthesised and labelled with $^{123}$I at the Paul Scherrer Institute (Villingen, Switzerland) according to the method described by Beer et al. 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. Images were obtained at 64 projections in a 64x64 matrix acquisition (pixel size: 8 mm) over 360°, 40 seconds for each projection (revolution time: 40 minutes). The acquired frames were corrected for the injected dose and for the individual distribution volume by normalising to 1.73 m body surface. The effective half life of iomazenil during SPECT acquisition was estimated by measuring the activity in a 60% isocontour at the start (mean of frame 1 to 3 during SPECT) and the remaining activity at the end of acquisition (last three planar images of the 64 projections).

200 MBq $^{123}$I iomazenil were given as a slow intravenous injection administered to the subject in a dimly lit, quiet room. As rCBF has only minor effects on delayed images of iomazenil binding SPECT imaging started 120 minutes postinjection. To avoid circadian variability, the SPECT scans for all subjects were obtained at the same time of day (+30 minutes). Directly after finishing $^{123}$I iomazenil SPECT Tc-99m ECD was injected in the same subjects to measure regional cerebral blood flow excluding blood flow effects in iomazenil distribution and binding.

All subjects underwent MRI on a Siemens 1.5 Tesla system using the standard head coil. 10 contiguous T1 weighted axial images (thickness: 4 mm, gap size: 0.3) were acquired up to planes parallel to the AC-PC line and coregistered with SPECT within the Siemens system to aid anatomical localisation and to exclude medium to severe brain atrophy, which was recently shown to significantly reduce r-CBF, RMIRGlu values, and receptor density.

Images were reconstructed by filtered back projection using a Butterworth filter of order 7 and a cut off frequency of 0.6 cm$^{-1}$. Transverse slices were reoriented 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 (full width half maximum (FWHM)) in the transaxial plane. Sixty four axial slices (exclusion of the most basal and the most dorsal slices), 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 a uniform linear attenuation correction coefficient of 0.12 cm$^{-1}$. Regions of interest (ROIs) were determined using the anatomical atlases of Talairach and Tournoux and Kretschmann and Weinrich; corresponding ROIs of all slices were summed together and defined 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 frontal cortex (which encompass the sensorimotor cortex), and upper medial and lateral prefrontal cortex, each on the right and left hemisphere. All ROIs were larger than...
Table 1  Iomazenil binding (means (SD)) in catatonic patients, and psychiatric and healthy controls

<table>
<thead>
<tr>
<th>ROI</th>
<th>HEM</th>
<th>Ratio</th>
<th>Catatonic patients (n=10)</th>
<th>Psychiatric controls (n=10)</th>
<th>Healthy controls (n=20)</th>
<th>p (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper</td>
<td>R</td>
<td>O</td>
<td>0.62 (0.02)b</td>
<td>0.64 (0.03)</td>
<td>0.68 (0.02)</td>
<td>0.001</td>
</tr>
<tr>
<td>Frontal</td>
<td>W</td>
<td>O</td>
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<td>0.73 (0.03)</td>
<td>0.77 (0.02)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lower</td>
<td>W</td>
<td>O</td>
<td>0.90 (0.03)ab</td>
<td>0.95 (0.03)</td>
<td>0.96 (0.03)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Statistical Analysis

Regional differences between groups were calculated using repeated measures analysis of variance (ANOVA) with one between subjects factor (groups) and two within subjects factors (regions of interest, level (upper, middle, lower)) and Bonferroni corrections for multiple comparisons.

Right-left differences were calculated in three ways: (1) 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)); (2) right-left differences for each region of interest were analysed in univariate t tests; (3) regions of interest were combined in a multivariate analysis for global right-left effects separately for each group and each level. A principal component test was used.32

Relations between clinical/psychopathological data and iomazenil binding in the various regions of interest were calculated using parametric Pearson correlations.

Results

IOMAZENIL BINDING

Catatonic patients showed significantly lower iomazenil binding in the left upper frontal cortex (which predominantly encompasses the sensorimotor cortex) than psychiatric (p<0.001) and healthy (p<0.001) controls (table 1 and figure). Both catatonic patients and psychiatric controls showed significantly lower iomazenil binding in the right and left lower (and upper) prefrontal cortex (p<0.001) than healthy controls (table 1. Iomazenil binding in parietal and temporal cortex7 and cerebellum did not differ significantly between groups.

Global right-left differences were significant at the lower and upper level in catatonia (p=0.0001–0.004) and in the lower level in psychiatric controls (p=0.0001) whereas there were no significant right-left differences in healthy controls. Regional right-left alterations were significant (p<0.001) in the upper frontal cortex and lower medial and lateral prefrontal cortex in catatonia and in the lower medial and lateral prefrontal cortex (but not in the upper frontal cortex) in psychiatric controls. Unlike healthy controls, both catatonic patients and psychiatric controls showed right-left differences in the lower medial and lateral prefrontal cortex. This is further underlined by calculation of right-left differences in multivariate analysis. Significant effects of regions (F=15.958; df=4.00; p=0.000), levels (F=12.519; df=3.00; p=0.000), and groups (F=6.927; df=3.00; p=0.001) were found. The level by group interaction (F=4.059; df=6.00; p=0.002) and the region by group interaction (F=2.390; df=8.00; p=0.034) were significant.

PERFUSION (r-CBF)

Values that differed between groups are shown in table 2. r-CBF in the left upper frontal cortex was significantly lower in catatonia (p<0.001) than in healthy controls, and the lower level was significantly lower in psychiatric controls (p<0.001) compared to healthy controls. A principal component test was used to evaluate regional differences between groups and to determine significant differences. Significant effects of regions (F=15.958; df=4.00; p=0.000), levels (F=12.519; df=3.00; p=0.000), and groups (F=6.927; df=3.00; p=0.001) were found. The level by group interaction (F=4.059; df=6.00; p=0.002) and the region by group interaction (F=2.390; df=8.00; p=0.034) were significant.

2.5×FWHM (15 mm) of our camera to allow a secure quantification.28

Average counts per pixel from each region were used for analysis. The activity measured in each ROI was divided by the activity obtained from the occipital maximum (occipital ratio), which corresponds to the 80% isocontour of the maximum value in the respective slice. The occipital maximum was obtained by averaging occipital activity from all slices.29 We used the occipital maximum and not the cerebellum as a reference region as in catatonia the cerebellum may itself be abnormal.30 31

Comparison of occipital maxima between catatonic patients and the other groups showed no significant differences (p>0.05). In addition to occipital ratios, we calculated whole brain ratios. Activities from each ROI were therefore normalised by dividing them by whole brain activity which by itself was obtained as averaged counts of all reconstructed slices in the brain.

All images were analysed blindly by two independent raters (CZ; RS). The intraobserver variability determined for single ROIs in all groups was lower than 3% (<1 SD of the ROI values). The interobserver variability for single ROIs in 20 patients was <4% (<1SD). All ROI values showed no significant deviations from normal distribution (Shapiro-Wilks test, p>0.05) so that differences of more than 2 SD between the three groups were considered abnormal. Intrarater and interrater reliabilities were evaluated and Kendall’s coefficients of correlation were found to be above 0.87.
cortex did not differ between groups. Catatonic patients showed significantly (p<0.001) lower r-CBF in the right lower and middle prefrontal (medial and lateral) cortex as well as in the lower parietal cortex than psychiatric and healthy controls (table 2). In addition, catatonic patients showed significantly (p<0.001) right lower r-CBF than healthy controls (table 2) in the 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.

Global right-left differences were significant at the lower level in healthy controls (p=0.000–0.012) and at all levels (upper, middle, lower) in catatonic patients (p=0.000–0.023) whereas there were no significant right-left differences at any level in psychiatric controls. Catatonic patients showed significant (p<0.001) right-left alterations in the lower and middle medial and lateral prefrontal cortex as well as in the lower parietal cortex whereas in healthy controls significant right-left differences were found only in the prefrontal but not in the parietal cortex. This is further underlined by calculation of right-left differences in multivariate analysis. Significant effects of regions (F=12.44; df=4.00; p=0.000) and groups (F=10.95; df=2.43; p=0.005) were shown. The group by region interaction was significant (F=3.14; df=8.88; p=0.006).

**CORRELATIONS**

Iomazenil binding in the left upper frontal cortex correlated significantly positive (r=0.662–0.766; p=0.010–0.049) with severity (NCs-mot, NCSbeh, NCStot, Rosebush) and duration (r=0.699; p=0.024) of catatonic (motor and behavioural) symptoms. Significant correlations were found between iomazenil binding in right lower lateral prefrontal cortex and severity (NCs-mot) and duration of motor symptoms in catatonia (r=0.711–0.784; p=0.017–0.007). In addition, significant negative correlations (r=−0.691; p=0.033) were found between anxiety (HAM-A) and iomazenil binding in the left upper frontal cortex as well as between depressive (HAM-D) symptoms and iomazenil binding in the right lower lateral prefrontal cortex in catatonic patients (r=−0.692; p=0.027) but not in psychiatric controls.

By contrast significant negative correlations between affective symptoms (HAM-A, HAM-D) and iomazenil binding in the left

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**Table 2** Mean r-CBF (mean (SD)) in catatonic patients, psychiatric and healthy controls

| ROI                  | HEM | Ratio | Catatonic patients (n=10) | Psychiatric controls (n=10) | Healthy controls (n=20) | p (17) |p
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Upper Medial Prefrontal</td>
<td>R O</td>
<td>0.75 (0.04)</td>
<td>0.75 (0.03)</td>
<td>0.76 (0.04)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Frontal L O</td>
<td>0.98 (0.06)</td>
<td>0.97 (0.04)</td>
<td>0.98 (0.05)</td>
<td>NS</td>
<td></td>
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<tr>
<td>Lateral W O</td>
<td>0.74 (0.05)</td>
<td>0.74 (0.04)</td>
<td>0.75 (0.04)</td>
<td>NS</td>
<td></td>
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<td>Prefrontal W O</td>
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<td>0.98 (0.05)</td>
<td>0.99 (0.03)</td>
<td>NS</td>
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<tr>
<td>Upper Medial Parietal</td>
<td>R O</td>
<td>0.73 (0.03)</td>
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<tr>
<td>Lower Medial Prefrontal</td>
<td>R O</td>
<td>1.01 (0.04)</td>
<td>1.01 (0.07)</td>
<td>1.04 (0.06)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Frontal L O</td>
<td>0.98 (0.03)</td>
<td>0.98 (0.04)</td>
<td>0.99 (0.04)</td>
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<td>Lateral W O</td>
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<tr>
<td>Prefrontal W O</td>
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<td>0.74 (0.04)</td>
<td>0.76 (0.03)</td>
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<tr>
<td>Upper Parietal W O</td>
<td>1.01 (0.03)</td>
<td>1.02 (0.03)</td>
<td>1.02 (0.04)</td>
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<td>Lower Parietal W O</td>
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<td>Middle Medial Prefrontal</td>
<td>R O</td>
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<td>0.70 (0.05)c</td>
<td>0.75 (0.04)</td>
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<tr>
<td>Lower Prefrontal W O</td>
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<tr>
<td>Lower Medial Prefrontal</td>
<td>R O</td>
<td>1.01 (0.05)</td>
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<td>Lower Medial Prefrontal</td>
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<td>1.01 (0.05)</td>
<td>1.02 (0.04)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as for table 1.
Decreased density of GABA-A receptors in akinetic catatonia

lower prefrontal cortex \((r=-0.678 \pm 0.088; p=0.031 \pm 0.005)\) were shown only in psychiatric controls but not in catatonic patients. Psychiatric controls did not show any significant correlations between psychopathological scores and iomazenil binding in the left upper frontal cortex.

Right lower parietal r-CBF correlated significantly negative with motor (NCSmot) \((r=-0.739; p=0.020)\) and affective (NCSaff, HAM-D) \((r=-0.716/0.725; p=0.015/0.019)\) symptoms in catatonic patients. Psychiatric controls showed significantly negative correlations between r-CBF in the right lower (medial and lateral) prefrontal cortex and depressive symptoms (HAM-D) \((r=-0.649-0.732; p=0.003-0.001)\).

**Discussion**

The main findings in the present study are the following: (1) significantly lower iomazenil binding with significant right-left alterations in the left sensorimotor cortex in catatonia; (2) significantly reduced r-CBF and significant right-left alterations in the right lower frontal and parietal cortex in catatonia; (3) significant relations of motor and affective symptoms in catatonia with left upper frontal and right lower prefrontal cortical iomazenil binding as well as with right lower parietal r-CBF.

Several studies showed immediate therapeutic effects of lorazepam, a GABA-A potentiator, in akinetic catatonia.\(^5\)\(^7\) We therefore assumed alterations in density of GABA-A receptors in cortical motor and premotor areas in pathophysiology of akinesia in catatonia.\(^4\)\(^7\)\(^14\) The present study showed reduced iomazenil binding and altered right-left relations in the left sensorimotor cortex in akinetic catatonia suggesting a decrease in the density of GABA-A receptors in the primary motor cortex. This finding is further supported by the following observations: (1) no reduction of r-CBF in the left sensorimotor cortex so that effects of r-CBF on iomazenil binding are rather unlikely; (2) reversal of therapeutic effects of lorazepam on akinesia by GABA-A antagonists (for example, Ro 15–1788) with reoccurrence of catatonic symptoms;\(^17\) (3) therapeutic efficacy of electroconvulsive therapy in akinetic catatonia which, similarly to benzodiazepines, is sought to act via the GABA system;\(^24\) (4) injection of GABA-A receptor agonists (for example, muscimol) into the motor cortex in monkeys leads to catatonic-like alterations in movements (akinesia, posturing) which could be reversed by GABA-A antagonists (for example, bicuculline).\(^36\)\(^38\) (5) delayed (within 2–4 hours) therapeutic effects of amantadine in akinetic catatonia\(^38\) which, via blockade of excitatory NMDA-receptors, indirectly strengthens cortical inhibition.

In addition, we found an opposite relation of motor and affective symptoms in catatonia with left sensorimotor cortical iomazenil binding. Motor symptoms correlated positively whereas affective alterations showed negative correlations. Considering the positive correlation, therapeutic effects of lorazepam in catatonia seem rather paradoxical as increase of GABA-ergic mediated inhibition should then go along with an increase of motor symptoms. However, affective catatonic symptoms showed an inverse correlation with sensorimotor and prefrontal cortical iomazenil binding so that lorazepam may modulate motor symptoms and GABA-ergic function in the motor cortex via affective and prefrontal GABA-ergic regulation.\(^49\) Such an assumption of a close pathophysiological relation between motor and affective symptoms in catatonia would be supported by the following observations: (1) significant correlations of affective and motor symptoms with both prefrontal and frontal cortical iomazenil binding in catatonia; (2) a close relation between efficaciously and movements in subjective experience of akinetic catatonic patients who, unlike parkinsonian patients, retrospectively report rather about intense and uncontrollable anxieties than about movement disturbances;\(^1\) lorazepam shows immediate therapeutic efficiency only in catatonic patients with strong emotional alterations whereas those with less affective symptoms do not respond to lorazepam.\(^5\)\(^7\)

Similarly to other studies\(^31\)\(^–\)\(^41\) we found deficits of r-CBF in the right parietal cortex\(^41\)\(^43\) which, in addition, correlated significantly with catatonic motor and affective symptoms. The parietal cortex has been found to be involved in motor attention and preparation of movements\(^44\)\(^–\)\(^46\) both showing specific alterations in catatonia: (1) catatonic patients are not aware of movement disturbances whereas they are fully aware of emotional alterations which may be interpreted as a deficit in motor attention; (2) catatonic patients show deficits in the preparation of movements;\(^3\) (3) observation of catatonic-like posturing in patients with isolated lesions in right parietal cortex\(^47\)\(^48\); (4) significant impairment in visual-spatial functions as measured with the visual-spatial object perception test, which is particularly sensitive to right parietal cortical lesions, in catatonia.\(^49\)

However, the exact pathophysiological relation of r-CBF deficits in the right parietal and right prefrontal cortex with decreased iomazenil-binding in the left sensorimotor cortex remains unclear so that specific investigation of motor attention and preparation is necessary in catatonia.