Cortical sulcal enlargement in catatonic schizophrenia: a planimetric CT study

Georg Northoff[a,*], Hagen Waters[b], Ingeborg Mooren[b], Uwe Schlüter[b], Silvia Diekmann[a], Peter Falkai[c], Bernhard Bogerts[a]

[a]*Department of Psychiatry, University of Magdeburg, Leipziger Straße 44, D-39120 Magdeburg, Germany*
[b]*Department of Psychiatry, University of Düsseldorf, Bergische Landstraße 2, D-40629 Düsseldorf, Germany*
[c]*Department of Psychiatry, University of Bonn, Sigmund-Freud-Straße, D-53105 Bonn, Germany*

Abstract

To determine whether patients with catatonic schizophrenia have specific alterations in brain morphology, internal (ventricles) and external (frontal, temporal, parieto-occipital) components of the cerebrospinal fluid (CSF) spaces were examined morphometrically. Planimetric measurements of computed tomographic (CT) scans from 37 patients with catatonic schizophrenia, 28 patients with hebephrenic schizophrenia, and 39 patients with paranoid schizophrenia, all diagnosed according to DSM-III-R criteria, were compared with separate age- and sex-matched non-psychiatric control groups, respectively. The areas of the frontal sulci, the parieto-occipital sulci, the inter-hemispheric fissure, and the lateral and third ventricles were measured separately for the right and left hemispheres. Catatonic patients showed significant enlargements in almost all CSF spaces, especially in the left fronto-temporal area which, in addition, correlated significantly with illness duraton. Hebephrenic patients showed selective enlargements in left temporal and left/right lower frontal cortical sulci, whereas paranoid schizophrenic patients showed no enlargements but significant correlations between left temporal cortical sulcal volume and illness duration. Alterations in temporal cortical areas were present in all three sub-types of schizophrenia. In addition to temporal alterations, hebephrenic schizophrenia was characterised by lower frontal (i.e. orbitofrontal) enlargement. Catatonic schizophrenia, the most severe sub-type with regard to clinical symptomatology and brain pathology, showed fronto-parietal cortical alterations.   © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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* Corresponding author: Tel.: +49-391-671-5029; fax: +49-391-671-5223.
E-mail address: georg.northoff@medizin.uni-magdeburg.de (G. Northoff)

1. Introduction

Kahlbaum (1874) introduced the term 'catatonia' to describe patients with a wide range of motor abnormalities including akinesia, posturing, catalepsy, rigidity, negativism, grimacing and waxy flexibility. Due to such alterations in patients' movements, catatonia has often been considered to have an organic etiology. The hypothesis of underlying organic alterations is further supported by post-mortem findings of qualitative and quantitative loss of tissue and volume in the basal ganglia, e.g. the striatum (Nagasaki, 1925; Hopf, 1954), the pallidum (Hopf, 1954; Bogerts et al., 1985; Stevens, 1986), and the nucleus accumbens (Nagasaki, 1925; Hopf, 1954). Furthermore, Stevens (1982) described periventricular and limbic alterations in catatonic schizophrenia. Recent investigations of cerebral blood flow in catatonic patients showed deficiencies predominantly in frontal and parietal cortical areas (Satoh et al., 1993; Liddle, 1994; Galynker et al., 1997; Northoff et al., 1998) as well as in the temporal cortex (Ebert et al., 1992). However, to our knowledge, no quantitative measurements of size of different cortical areas and cerebrospinal fluid (CSF) spaces have been carried out in catatonic schizophrenia. Computed tomographic (CT) studies showed mild atrophy of the cerebellum (Joseph et al., 1985; Wilcox, 1991), but these studies did not undertake systematic measurements of inner and outer CSF spaces.

The present CT study was performed to determine whether brain tissue alterations in catatonic schizophrenia affect the whole brain equally or are localised in certain brain regions. Previous volumetric studies in paranoid schizophrenia showed alterations in temporo-limbic areas that correlated significantly with positive symptoms (Degreef et al., 1992; Bogerts et al., 1993; Bogerts, 1997), whereas in residual schizophrenia with negative symptoms, frontal enlargements were reported (Raz, 1993; Rubin et al., 1993; Gur et al., 1994; Lim et al., 1996; Woods et al., 1996). Despite extensive morphometric investigations in schizophrenia, there has not previously been a study that quantitatively explored alterations specifically in catatonic schizophrenia. We therefore measured CSF spaces in CT scans obtained in patients with three sub-types of schizophrenia: catatonic, hebephrenic, and paranoid schizophrenia. Findings in the three sub-groups were compared with those in age- and sex-matched non-psychiatric control groups, respectively. On the basis of the findings reviewed above, it was hypothesised that the following types of alterations would be found: (i) fronto-parieto-temporal abnormalities in catatonic schizophrenia, an assumption based on the occurrence of catatonic-like symptoms in patients with fronto-parietal lesions as well as on findings of fronto-parietal regional cerebral blood flow deficits in catatonia (Dolan et al., 1993; Northoff, 1997; Northoff et al., 1998); (ii) temporal abnormalities in paranoid schizophrenia, an assumption based on findings of significant correlations between temporo-limbic alterations and positive symptoms in schizophrenia (Degreef et al., 1992; Bogerts et al., 1993); (iii) temporal and lower (i.e. medial/lateral orbito-frontal cortex) frontal abnormalities in hebephrenia, an assumption based on the observation of hebephrenic-like symptoms such as affective (medial orbito-frontal cortex) and behavioural (lateral orbito-frontal cortex) dis-inhibition in patients with lower frontal lesions (Milner and Petrides, 1984; Morecraft et al., 1992) and their similarity to the negative symptoms of schizophrenia (Andreasen, 1983).

Since volumetric determinations in relatively thick axial CT scan sections are difficult to perform, we used a previously described (Bogerts et al., 1987) planimetric technique to measure the size of the ventricles and cortical CSF components separately for frontal, temporal and parieto-occipital regions. Although this method is less advanced than quantitative volumetric magnetic resonance imaging, the availability of a large sample of catatonic schizophrenic patients investigated with uniformly performed CT scans is quite unusual. In addition, previous studies in paranoid schizophrenic (Bogerts et al., 1987) and depressive patients (Wurthmann et al., 1995; Baumann et al., 1997) showed that the planimetric method applied here yields valid and reliable results.

2. Methods

2.1. Subjects

2.1.1. Catatonic schizophrenia

CT scans of 37 patients with catatonic schizophrenia (28 women, nine men; age range: 21–63 years, mean age: 46.5 ± 8.9 years), hospitalised at the Department of Psychiatry at the University of Düsseldorf between 1992 and 1994, were investigated. Patients were included if they met DSM-III-R diagnostic criteria (American Psychiatric Association, 1987) and were older than 18 years and younger than 65 years. Isolated mutism or stupor were not considered as sufficient for the diagnosis of catatonia — in addition to stupor/mutism, patients had to show psychomotor and behavioural symptoms like akinesia, posturing, catalepsy, automatic obedience, negativism, and mannerisms such that, clinically, these patients could clearly be distinguished from paranoid and hebephrenic schizophrenic patients. Discharge diagnoses were performed by independent diagnosticians (inter-rater reliability: $r = 0.96$) who used a semi-structured interview based on DSM-III-R criteria. Illness duration varied between 1 and 32 years (mean: 7.2 ± 3.4 years).

2.1.2. Hebephrenic schizophrenia

CT scans of 28 patients with hebephrenic schizophrenia (14 women, 14 men; age range: 21–54 years, mean age: 23.9 ± 6.5 years), hospitalised at the Department of Psychiatry at the University of Düsseldorf, were investigated. Patients were included if they met DSM-III-R diagnostic criteria and were older than 18 years and younger than 65 years. All hebephrenic patients showed the characteristic affective abnormalities (i.e. emotional blunting) and could therefore be clearly distinguished from the catatonic and paranoid schizophrenic groups which both did not show any signs of emotional blunting. Discharge diagnoses were made by independent diagnosticians (inter-rater reliability: $r = 0.97$) who used a semi-structured interview based on DSM-III-R criteria. Illness duration ranged between 0 and 6 years (mean: 4.3 ± 2.4 years).

2.1.3. Paranoid schizophrenia

CT scans of 39 patients with paranoid schizophrenia (29 women, 10 men; age range: 21–58 years, mean age: 41.2 ± 7.6 years), hospitalised at the Department of Psychiatry at the University of Düsseldorf, were investigated. Patients were included if they met DSM-III-R diagnostic criteria and were older than 18 years and younger than 65 years. All paranoid patients showed severe delusions and hallucinations (i.e. positive symptoms) and could therefore be clearly distinguished from catatonic and hebephrenic schizophrenic patients. Discharge diagnoses were made by independent diagnosticians (inter-rater reliability: $r = 0.98$) who used a semi-structured interview based on DSM-III-R criteria. Illness duration ranged between 1 and 25 years (mean: 6.9 ± 3.1 years).

2.1.4. Non-psychiatric controls

Each schizophrenic sub-group was compared with an age- and sex-matched separate non-psychiatric control group, respectively. The CT scans from catatonic patients were compared with those of 37 age- and sex-matched non-psychiatric controls (28 women, 9 men; age range: 20–64 years; mean age: 45.5 ± 7.1 years). The CT scans from hebephrenic patients were compared with those of 28 age- and sex-matched non-psychiatric controls (14 women, 14 men; age range: 18–31 years, mean age: 23.9 ± 5.9 years). The CT scans from paranoid patients were compared with those of 39 age- and sex-matched non-psychiatric controls (29 women, 10 men; age range: 21–59 years, mean age: 41.1 ± 6.8 years). Non-psychiatric control CT scans were obtained prospectively and randomly selected from neurological and surgical patients with peripheral vertigo, peripheral dysopia, skull contusion and commotio cerebri. Control subjects underwent CT scan to exclude a central nervous system lesion as a cause of their symptoms. Scans from healthy controls were assessed as 'normal CT' by radiologists.

2.1.5. Exclusion criteria

All schizophrenic patients were treated with haloperidol in standard doses (range: 5–35 mg; no differences between the three schizophrenic

sub-groups) for a duration of 6.8 ± 2.9 years (means $\pm$ S.D.) in catatonic patients, of 4.2 ± 2.1 years (means $\pm$ S.D.) in hebephrenic patients, and of 6.7 ± 2.9 years (means $\pm$ S.D.) in paranoid patients. Schizophrenic patients with a history of drug and alcohol abuse, head injury and/or additional co-morbid disease were excluded. Five catatonic patients had received earlier electroconvulsive therapy (ECT), but their CT-scan measurements did not differ from those of patients who had not been treated with ECT. Most patients had been hospitalised on a number of occasions (catatonic patients: 5.4 ± 2.1; hebephrenic patients: 2.3 ± 1.2; paranoid patients: 4.1 ± 2.4; means $\pm$ S.D.) and many of them had a positive family history of schizophrenia.

Non-psychiatric controls with a history of cancer, chemotherapy, alcoholism, addiction and any kind of psychiatric disease were excluded.

The scans of schizophrenic and healthy subjects were obtained between 1992 and 1994 in the Department of Radiology, Marienhospital, Düsseldorf. Qualitative assessment by a radiologist and psychiatrist experienced in neuroradiology (B.B.) determined that none of the scans revealed any macroscopic brain tissue damage. Before they entered the study, all patients and control subjects underwent a physical examination, laboratory tests, and an electroencephalographic examination. None of them suffered from somatic or neurological abnormalities other than dizziness or concussion (in normal control subjects). All investigations were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. Procedures

CT scans were performed on a third generation Siemens Tomoscan 300. Planimetric measurements of CSF spaces were performed according to the methodology described by Bogerts et al. (1987) and Wurthmann et al. (1995). From each brain, eight transversal sections (15% to the orbito-meatal line, 9-mm distance between each section) were obtained. All sections were enlarged by overhead projection ($4 \times$), and all visible inner and outer CSF spaces were delineated manually and their areas measured by planimetry. After identical delineation criteria had been established, different levels of all CT scans were evaluated simultaneously by two of the authors, each of whom delineated ventricles and outer CSF spaces on another section. Each schizophrenic sub-group, together with the respective non-psychiatric control group, was evaluated by different researchers. Catatonic patients and their controls were measured by H.W./P.F., hebephrenic patients and their controls by U.S./B.B., and paranoid patients and their controls by I.M./P.F. Measurements were performed without knowledge of the subject's diagnostic group. Test−retest reliability was established by remeasuring 10 CT scans from each group 3 months later. Assessment of the intra-rater ($r = 0.71−0.99$) and inter-rater ($r = 0.71−0.99$) reliabilities for the various parameters in CT scans revealed correlation coefficients between 0.71 (third ventricle) and 0.99 (ventricle−brain ratio).

The following parameters were measured: (a) the ventricle−brain ratio (VBR, area of the lateral ventricles at their largest extent in percent of the whole brain area at that level) was calculated from the slice exhibiting the largest area of lateral ventricles; (b) the area and diameter of the third ventricles at their widest extent were determined and calculated as percent of the total area on the VBR level; (c) the sum of all frontal; and (d) parieto-occipital sulci, respectively, was calculated in percent of the whole brain area at the ventricular level in the four most dorsal sections. The border between frontal and parieto-occipital areas was defined by the sulcus centralis; (e) the relative area of the inter-hemispheric fissure was expressed as a percentage of whole brain area at the VBR level; (f) the area of temporal sub-arachnoidal space including the Sylvian fissure was divided into left and right portions at four different levels (for more detailed definition of the temporal levels, see Bogerts et al., 1987); (g) the areas of the left and right frontal and parieto-occipital CSF spaces were measured below the VBR level; and (h) the areas of fronto-sagittal CSF spaces were measured in the four basal

levels. The fourth ventricle, the cerebellar sulci, the cisternae chiasmatis and the vena galeni were not included in the measurements.

2.3. Statistical analysis

Each schizophrenic sub-group was statistically compared with its respective non-psychiatric control group. Since the schizophrenic sub-groups differed in mean age and were measured by different raters, they could not be compared directly. *T*-tests with Bonferroni corrections over the 21 regions ($P < 0.05 = 0.002$; $P < 0.01 = 0.0005$) were used for comparisons of the various regions between the schizophrenic sub-groups and their respective non-psychiatric control group separately for each schizophrenic sub-group. Multivariate analysis of variance (MANOVA; diagnosis × gender) was performed for analysis of gender effects (covaried for age) with the statistical package BMDP 7d. To address the question of asymmetry of the structural changes, a right–left comparison of sulcal enlargement was performed by calculating the so-called Galaburda index: $2 \times$ (left−right)/(left + right/100). In addition, a multivariate analysis of variance (MANOVA; diagnosis × right/left) was performed for analysis of right/left effects (covaried for age) with the same statistical package. For correlations with age and duration of illness, the software package BMDP 6R (Pearson linear correlations) was used.

3. Results

3.1. CSF spaces (see Table 1)

3.1.1. Catatonic schizophrenia
Catatonic patients showed highly significant enlargements of basal and upper parasagittal CSF spaces as well as of the diameter and the area of the third ventricle (Table 1). There were significant enlargements in catatonic patients in the upper parts of the left and right frontal cortical sulci as well as in the left and right second and third temporal levels. Marginally significant enlargement was seen in right occipital sulci, right

second temporal level, right fourth temporal level and right fronto-basal sulci (Table 1). There were no significant changes in the following areas: left occipital, right and left basal-occipital sulci, left first temporal level and left fronto-basal sulci. In addition we found neither significant gender nor right/left differences in any of the measured parameters in catatonic schizophrenia. In summary, catatonic patients showed a diffuse enlargement in almost all CSF spaces that was most pronounced with a loss of 'normal' asymmetry in fronto-temporal regions.

3.1.2. Hebephrenic schizophrenia
Hebephrenic schizophrenic patients showed significant enlargements of the diameter of the third ventricle, of the left first, second, third, and fourth temporal levels, of the right fourth temporal level, and of the right and left lower parts of the frontal cortical sulci (Table 1). Neither the upper frontal cortical sulci nor the third ventricle (diameter, VBR) differed significantly between hebephrenic schizophrenic patients and healthy controls. We found no significant gender differences in hebephrenic schizophrenia. The Galaburda index differed significantly between hebephrenic schizophrenic patients and healthy controls in the second ($P = 0.0256$) and fourth ($P = 0.0369$) temporal level. MANOVA revealed a significant P value for a diagnosis-right/left interaction on the second ($F = 10.23$; d.f. = 2,35; $P = 0.034$) and the fourth ($F = 9.58$; d.f. = 3,67; $P = 0.045$) temporal levels. In summary, hebephrenic schizophrenic patients showed circumscribed enlargements in lower frontal and temporal areas with significant right/left differences (i.e. enlargements on the left side) compared with non-psychiatric controls (i.e. hebephrenic patients showed greater asymmetry).

3.1.3. Paranoid schizophrenia
There were no significant differences in CSF spaces between paranoid schizophrenic patients and non-psychiatric controls. The VBR was larger in paranoid schizophrenic patients than in healthy controls (Table 1), but the difference did not reach the level of statistical significance ($P =$

Table 1
Mean values[a] (mean ± S.D.)[b] of inner and outer CSF spaces, cortical areas, and sulci with t-values from statistical analyses (t-tests)[c]

	Cat. Schiz.[n] (n = 37)	Controls (n = 37)	t	Hebeph.Schiz.[o] (n = 28)	Controls (n = 28)	t	Para.Schiz.[p] (n = 39)	Controls (n = 39)	t
VBR[d]	8.26 (2.70)	5.96 (2.34)	4.95**	6.46 (3.22)	5.95 (4.22)	1.21	7.20 (3.24)	5.90 (3.65)	0.45
3. Vd[e]	6.90 (1.85)	5.40 (1.40)	4.87**	5.64 (1.76)	4.60 (2.43)	3.76*	5.65 (1.85)	5.16 (1.78)	0.79
3. Vfl.[f]	0.95 (0.32)	0.69 (0.22)	5.02**	1.55 (1.25)	1.09 (0.46)	0.87	1.53 (5.95)	1.32 (7.68)	1.23
Sf l[g]	1.80 (1.85)	0.59 (1.40)	5.09**	0.92 (1.31)	0.58 (0.57)	0.65	0.78 (1.20)	0.69 (0.58)	0.49
Sf r[g]	2.88 (1.33)	0.61 (0.71)	4.76*	0.75 (0.87)	0.71 (0.75)	0.78	0.71 (0.85)	0.76 (0.71)	1.36
Spo l[h]	0.88 (0.95)	0.45 (0.55)	1.03	0.75 (1.06)	0.47 (0.78)	0.98	0.65 (1.02)	0.59 (0.89)	1.82
Spo r[h]	0.89 (0.85)	0.45 (0.50)	2.79*	0.62 (1.00)	0.30 (0.89)	1.03	0.63 (1.02)	0.58 (0.54)	1.69
Paras[i]	9.26 (3.69)	5.90 (3.26)	4.86**	6.50 (3.33)	4.20 (2.90)	1.65	5.56 (2.40)	4.90 (2.85)	0.47
Temp 1 l[j]	0.25 (0.48)	0.14 (0.22)	0.76	1.17 (1.92)	0.29 (0.61)	3.42*	0.89 (1.02)	0.56 (0.58)	1.59
Temp 1 r[j]	0.26 (0.29)	0.08 (0.14)	3.99**	0.73 (1.14)	0.25 (0.98)	1.07	0.89 (0.74)	0.76 (0.56)	1.34
Temp 2 l[j]	0.73 (0.76)	0.28 (0.30)	4.56**	4.57 (4.31)	1.75 (2.80)	3.54*	2.67 (1.05)	2.65 (1.20)	1.52
Temp 2 r[j]	0.47 (0.45)	0.19 (0.16)	2.76*	2.36 (3.21)	1.47 (2.43)	0.76	1.89 (2.20)	1.69 (1.90)	0.79
Temp 3 l[j]	1.17 (0.86)	0.64 (0.50)	3.55*	6.23 (4.17)	3.87 (3.54)	3.21*	2.89 (4.20)	2.98 (3.20)	1.29
Temp 3 r[j]	0.97 (0.82)	0.93 (0.41)	3.45*	3.96 (2.40)	3.35 (3.54)	1.21	3.80 (2.48)	3.75 (2.50)	0.63
Temp 4 l[j]	0.99 (0.76)	0.52 (0.35)	3.21*	2.93 (4.22)	0.18 (0.52)	3.56*	4.37 (6.58)	2.38 (3.25)	1.46
Temp 4 r[j]	0.99 (0.68)	0.62 (0.39)	2.56*	1.98 (3.06)	0.50 (1.68)	3.68*	1.69 (2.85)	0.89 (1.01)	1.83
Sfb l[k]	1.70 (1.15)	1.21 (0.62)	1.23	1.83 (1.27)	1.00 (0.89)	4.76**	1.25 (1.05)	1.20 (0.90)	0.92
Sfb r[k]	1.79 (1.36)	0.90 (0.46)	2.86*	1.63 (0.91)	0.64 (0.60)	5.79**	1.02 (0.98)	0.89 (0.50)	0.86
Spob l[l]	0.04 (0.12)	0.07 (0.18)	1.21	0.95 (2.20)	0.30 (0.94)	1.23	0.78 (1.20)	0.60 (0.40)	1.59
Spob r[l]	0.07 (0.15)	0.10 (0.10)	0.96	0.48 (1.14)	0.07 (0.24)	1.52	0.25 (1.02)	0.15 (0.25)	1.24
Paras b[m]	6.30 (2.31)	4.03 (1.77)	4.89**	5.02 (4.20)	4.20 (1.95)	0.69	4.21 (1.98)	3.95 (1.59)	1.63

[a] Mean planimetric values of CSF spaces expressed as ratio (%) to whole brain area.
[b] S.D. = standard deviation (%).
[c] t-Tests with Bonferroni correction for multiple comparisons ($P < 0.05 = 0.002$; $P < 0.01 = 0.0005$).
[d] VBR = ventricular brain ratio.
[e] 3.VD = diameter of the third ventricle.
[f] 3.Vfl = area of the third ventricle.
[g] Sf l/r = left/right frontal sulci of four upper levels.
[h] Spo l/r = left/right parieto-occipital sulci of four upper levels.
[i] Paras = parasagittal space.
[j] Temp 1–4 l/r = left/right temporal levels 1–4.
[k] Sfb l/r = left/right frontal sulci of four lower levels.
[l] Spob l/r = left/right parieto-occipital sulci of four lower levels.
[m] Paras b = fronto-basal parts of parasagittal space.
[n] Cat.Schiz. = catatonic schizophrenia.
[o] Hebeph.Schiz. = hebephrenic schizophrenia.
[p] Para.Schiz. = paranoid schizophrenia.
* = $P = 0.05$; ** = $P = 0.005$.

0.085). We found neither significant gender nor right/left differences in patients with paranoid schizophrenia.

In summary, paranoid schizophrenic patients showed no significant enlargements in any of the CSF spaces measured compared with non-psychiatric controls.

3.2. Correlation of age and illness duration with CSF spaces

3.2.1. Catatonic schizophrenia

There were significant positive correlations between CSF parameters in CT (except right fourth temporal level and right parieto-occipital basal sulci) and age with correlation coefficients (r) of $r = 0.304$–0.534 and $P = 0.005$–0.05. The correlation coefficients were highest in temporal areas and lowest in upper parieto-occipital sulci. Furthermore, we found a significant positive correlation between illness duration and age ($r = 0.548$; $P < 0.001$). We correlated CT parameters with illness duration even parcelling out age effects. There were significant positive correlations of illness duration with left frontal sulci ($r = 0.36$; $P < 0.05$), left first ($r = 0.59$; $P < 0.005$) and second ($r = 0.51$; $P < 0.005$) temporal sulci including Sylvian fissure, left parieto-occipital sulci ($r = 0.31$; $P < 0.05$) and left parieto-occipital basal ($r = 0.49$; $P < 0.005$) sulci. In summary, catatonic patients showed a relationship between illness duration and left hemispheric cortical sulcal enlargement, especially of left fronto-temporal areas, indicating that changes in these areas may be progressive.

3.2.2. Hebephrenic schizophrenia

Significant positive correlations were found between the right first temporal level and age ($r = 0.39$; $P < 0.05$). Furthermore, the right ($r = 0.43$; $P < 0.05$) and left ($r = 0.41$; $P < 0.05$) fourth temporal levels showed significant positive correlations with illness duration when age effects were parcelled out. In summary, there is a relationship between illness duration and CSF spaces in right and left lower temporal areas in hebephrenic schizophrenia.

3.2.3. Paranoid schizophrenia

The right ($r = 0.24$; $P < 0.01$) and left ($r = 0.29$; $P < 0.01$) first temporal levels as well as the right second temporal level ($r = 0.38$; $P < 0.001$) showed significant positive correlations with age. The left first temporal level correlated significantly ($r = 0.24$; $P < 0.01$) with illness duration even when the effects of age were parcelled out. In summary, the left upper temporal level is closely related to illness duration in paranoid schizophrenia.

4. Discussion

The major findings in this study are the followings: (a) diffuse enlargements in almost all inner and outer CSF spaces and sulci except the occipital region in catatonia; (b) significant positive correlations of illness duration with volumes of CSF surrounding the left hemisphere, most pronounced in left fronto-temporal areas, in catatonia; and (c) significant positive correlations of illness duration with CSF volumes of temporal areas in paranoid and hebephrenic schizophrenic patients.

Since to our knowledge there are no other morphometric CT or MRI studies comparing different brain regions in patients with catatonic schizophrenia, we focus the discussion on the comparisons among the three schizophrenic subtypes as well as on the role of fronto-temporal cortical alterations in the pathophysiology of psychomotor symptoms in catatonic schizophrenia.

4.1. Fronto-parietal and temporal–cortical alterations in catatonic schizophrenia

Patients with catatonic schizophrenia, in addition to alterations in fronto-temporal cortical CSF spaces, showed diffuse enlargements in almost all other cortical sulci. Subtle fronto-temporal and ventricular enlargements have been reported in CT and MRI studies in patients with schizophrenia (Bogerts et al., 1987; Raz, 1993; Rubin et al., 1993; Gur et al., 1994; Falkai and Bogerts, 1995; Turetsky et al., 1995; Cowell et al., 1996; Woods et al., 1996) which, in contrast to our findings in

catatonic schizophrenia, were largely restricted to frontal and temporal cortical sulci whereas parietal and occipital CSF spaces were not affected. In the present results, catatonic schizophrenia was characterised by diffuse enlargements in almost all cortical sulci and, compared with paranoid and hebephrenic schizophrenia, may therefore be considered to represent the most severe schizophrenic sub-type in both acute clinical symptomatology and underlying brain pathology, entirely independent of prognosis.

In addition, there were significant correlations between illness duration and fronto-temporal cortical sulcal enlargements in catatonic schizophrenia. Fronto-temporal alterations may be closely related to the pathophysiology of catatonic symptoms, as is also suggested by findings of decreased regional cerebral blood flow (rCBF) in fronto-parietal and temporal cortex in catatonia (Ebert et al., 1992; Satoh et al., 1993; Northoff et al., 1998). The exact relationship between catatonic symptoms and fronto-temporal enlargements, however, remains unclear. Similar to positive symptoms in paranoid schizophrenia (Degreef et al., 1992; Bogerts et al., 1993), alterations in temporal–cortical sulci may be closely related to acute psychotic symptoms since catatonic schizophrenic patients often show intense paranoid delusions and acoustic hallucinations. In contrast, fronto-parietal alterations in catatonic patients may be related to psychomotor poverty symptoms like akinesia, stupor, mutism, posturing and catalepsy, which would be in accord with findings of reduced frontal activation during a motor task in patients with a psychomotor poverty syndrome (Dolan et al., 1993) and catatonia (Northoff et al., 1999) as well as with lesion studies (Lohr and Wiesniewski, 1987; Northoff, 1997). One may also speculate about specific alterations in functional connectivity between temporal and frontal–cortical areas in catatonic schizophrenia, but this issue needs to be investigated separately in activation studies with functional imaging.

4.2. Temporal cortical alterations in hebephrenic and paranoid schizophrenia

Unlike catatonic schizophrenia, hebephrenic schizophrenia was characterised by enlargements that were restricted to temporal and lower frontal cortical sulci — a pattern resembling findings in patients with residual schizophrenia who showed predominant negative symptoms (Gur et al., 1994; Falkai and Bogerts, 1995; Woods et al., 1996). Symptomatic overlap between residual and hebephrenic schizophrenia with regard to the occurrence of negative symptoms (Andreasen, 1983) may account for such enlargements in almost similar cortical sulci. Such a hypothesis, however, is purely speculative since we did not investigate patients with residual schizophrenia in the current study.

The lower frontal cortex includes predominantly the orbito-frontal cortex which, functionally, can be associated with affective control (medial orbito-frontal cortex) and behavioural organisation (lateral orbito-frontal cortex) (Morecraft et al., 1992). Disturbances of affective control and behavioural organisation may account for affective (i.e. emotional blunting) and behavioural (i.e. disorganisation) alterations observed in hebephrenic schizophrenia which would be in accordance with our finding of lower frontal (i.e. orbito-frontal) cortical sulcal enlargements in these patients. Such an assumption would be supported by findings of significant correlations between frontal lobe volume and behavioural disorganisation in patients with residual schizophrenia (Turetsky et al., 1995; Cowell et al., 1996). In addition to fronto-temporal enlargements, we found significant correlations between illness duration and lower temporal CSF space enlargements in hebephrenic patients. Consecutively, the temporal lobe may be specifically related to the disease process in hebephrenic schizophrenia which may account for its bad clinical prognosis. Furthermore, the lower temporal lobe is strongly connected with the lower frontal cortex, i.e. the orbito-frontal cortex (Morecraft et al., 1992), so that one may assume a possible disturbance of temporo-orbito-frontal functional connectivity in hebephrenia. However, further studies specifically investigating temporal and orbito-frontal cortical functions like affective control and behavioural organisation are necessary to elucidate the specific role of a disturbance in

temporo-orbito-frontal functional connectivity in hebephrenic schizophrenia.

In contrast to catatonic and hebephrenic schizophrenia, paranoid schizophrenia was not associated with significant enlargements but only with significant correlations between illness duration and temporal–cortical sulcal volume (see also Degreef et al., 1992; Bogerts et al., 1993). Positive symptoms as are observed in paranoid schizophrenia may be closely related to temporo-limbic alterations (Bogerts, 1997).

4.3. Methodological limitations

First, although the applied method of planimetric measurements of CT scans may have some disadvantages compared with volumetric measurements based on automatic grey level segmentation with MRI, this method has proved to be highly sensitive and reliable in the detection of enlargements in inner and outer CSF spaces (Bogerts et al., 1987; Wurthmann et al., 1995; Baumann et al., 1997). Furthermore, our results yielded high intra-rater and inter-rater measures of agreement that support the reliability of the applied method. Notwithstanding any methodological limitations of the CT measurements, the availability of a large sample of uniformly scanned catatonic schizophrenic patients is a valuable resource for data analysis. Nevertheless, the current study, which relied upon a relatively simple planimetric method, may be regarded as exploratory and should be followed by MRI studies with computerised volumetric measurements.

Second, the use of separate age- and sex-matched non-psychiatric control groups for each schizophrenic sub-type did not permit direct statistical comparison between the three sub-types. It had the advantage, however, of taking into consideration confounding variables such as age and sex.

Third, we were not able to include patients with residual schizophrenia in our study. Residual schizophrenic patients are in general older with a longer illness duration than paranoid patients. Although there were no significant differences in age and illness duration between catatonic and paranoid schizophrenic patients, the former

showed much more pronounced differences from non-psychiatric controls than the latter. The hebephenic patients were younger and had a shorter illness duration, but they nevertheless showed greater cortical-sulcal enlargement than paranoid patients.

Fourth, the three control groups consisted of neurological patients with no macroscopic brain anomalies (see Section 2). Thus, although the control subjects were non-schizophrenic and showed no structurally (i.e. macroscopically visible) brain disease, they were nevertheless not entirely healthy so that they must be considered as non-psychiatric controls rather than as healthy controls. It seems unlikely, however, that this methodological limitation could account for the differences in patterns of CSF enlargements between the three schizophrenic sub-types compared with their respective control groups.

Fifth, neuroleptic effects cannot be entirely excluded. However, all three schizophrenic groups were treated with the same neuroleptic medication (e.g. haloperidol) in similar dose ranges (see Section 2) so that they did not differ significantly with regard to neuroleptic treatment. It is, of course, possible that the neuroleptic medication could have had differential effects in the three schizophrenic subtypes and thus have accounted for the different types of brain abnormalities noted. Since the intensity of psychopathological symptoms was not rated, we were unable to correlate symptoms with CSF spaces which limits the interpretation of the present findings, especially with regard to their specifity for the respective schizophrenic sub-types.

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