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ORIGINAL PAPER

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Influence of genetic loading, obstetric complications and premorbid adjustment on brain morphology in schizophrenia: A MRI study

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Abstract Cerebrospinal fluid (CSF) space enlargement in schizophrenia is a prominent finding. This study was initiated to examine the influence of genetic loading, obstetric complications and premorbid adjustment on the extent of this enlargement.

The sample of this MRI study consisted of 40 schizophrenic patients, 24 psychiatric and 40 healthy family members from 10 uniaffected and 19 multiple affected families with schizophrenia, such as 27 control subjects from non-affected families. The ventricle-to-brain-ratio (VBR), and the areas of the third ventricle, sylvian fissure, temporal horn and interhemispheric fissure at the slice where these structures reached their maximum were examined relatively to the corresponding total brain areas. The sum of CSF areas was calculated as a parameter for global atrophy.

From MANCOVA adjusted for intervening variables the right VBR and the sum of CSF areas revealed significant differences between diagnostic groups. For these areas schizophrenic patients showed an increase compared to control subjects and family members with psychiatric disorder. Genetic loading influenced the interhemispheric fissure, enlarged in multiple affected compared to uniaffected families, and the temporal horn asymmetry, which was right sided (right > left) in control subjects and multiple affected families, but inverted in uniaffected families. Neonatal obstetric complications influenced only the size of the VBR, while premorbid adjustment predicted various CSF areas.

In conclusion, schizophrenic subjects from multiple and uniaffected families showed a global atrophy, which was most pronounced in the VBR. Genetic loading seems to have an impact on frontal regions as the interhemispheric fissure and on the temporal horn.

Key words familial schizophrenia · genetic loading · obstetric complications · VBR · temporal horn · interhemispheric fissure

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Introduction

Metaanalyses of the published MRI literature (Wright et al. 2000, Lawrie and Abukmeil 1998, Raz and Raz 1990) have convincingly shown ventricular enlargement and volume decrease of temporal lobe structures in schizophrenia. The etiology of these findings is unclear, but obstetric complications (OC) as described by Cannon et al. (1989, 1993) or an underlying genetic vulnerability are discussed as risk factors. Studying uniaffected and multiple affected families with schizophrenia is one possibility to explore the influence of these factors on brain morphology. There is an increasing number of publications studying the lateral ventricles, third ventricle, sylvian fissure (SF), temporal horn or interhemispheric fissure (Cannon et al. 1989, Staal et al. 2000, Silverman et al. 1998, Zorilla et al. 1997, Roy et al. 1994, Honer et al. 1995, Falkai et al. 2002) demonstrating structural changes in non-affected relatives with values intermediate between control subjects and family members suffering from schizophrenia. There is increasing literature analyzing which parts of the brain are determined by genetic influences on the one hand and by environmental factors

on the other hand (Thompson et al. 2001, Baare et al. 2001, Pfefferbaum et al. 2000). Genetic influences in schizophrenia were tried to establish demarcated from other psychiatric disorders (Lichtermann et al. 2001, Maier et al. 1999). The influence of OC and premorbid adjustment on brain morphology especially in multiple affected families have not yet been studied so far.

Therefore the VBR, the areas of the third ventricle, SF, temporal horn and interhemispheric fissure were determined on the 131 MRI scans available. These parameters were chosen as they have previously been helpful to distinguish between schizophrenic patients and controls or are situated in key regions for schizophrenia.

On the first sight volumetric analysis seems to be superior to area measurements. However, determining volume parameters is time consuming and the advantage is doubtful, since volumetric analysis is not always superior to area measurements. If there are similar changes in schizophrenia of a structure in all directions, volumetric analysis will show larger percental differences between the diagnostic groups than areal parameters, but there might be situations where areal analysis is more specific than volumetric measurements, e. g., when analyzing a coronal plane where the height and width decreases in schizophrenia while the length of that structure increases. Therefore the strategy of determining well-defined area measurements in a large cohort seems worthwhile in order to be able to search for those regions, where more detailed morphometry might be necessary. For this reason the VBR concept, calculating a CSF area as percentage of the total brain area at the slice where the structure reaches its maximum, has been transferred to other CSF areas for this study using coronal brain cuts.

The following hypotheses were set up:

- Schizophrenic subjects from uniaffected and multiple affected families with schizophrenia show a ventricular enlargement compared to control subjects. Family members without schizophrenia form an intermediate phenotype between their schizophrenic relatives and the control group. This order predominates in VBR and third ventricle area but it is also visible to a lesser extent in the other cerebrospinal fluid (CSF) areas measured.
- The genetic loading has an influence on the brain morphology. It is expressed as a difference between uniaffected and multiple affected families.
- OC have a modulating effect on the size of lateral ventricles. An influence on other CSF areas is not expected.

Methods

Patients and control subjects

The present analysis includes the data of 91 persons recruited at the Heinrich-Heine University Düsseldorf between 1995 and 1997, and of 40 persons recruited at the Friedrich-Wilhelms University Bonn between 1998 and 1999.

Diagnostically the sample consisted of 40 family members with schizophrenia or schizoaffective disorder (ICD-10: F20 (n = 29); F25 (n = 11)), 24 subjects with axis-I disorder other than schizophrenia (ICD-10: F0-F1 (n = 4); F21-F24 (n = 3); F3 (n = 3); F4 (n = 11); F5-F6 (n = 3)), 40 family members without any psychiatric diagnosis and 27 healthy control subjects from non-affected families.

There were 68 members from 19 multiple affected families (at least two schizophrenic subjects in different generations), 23 members from 10 uniaffected families (only one member suffered from schizophrenia over three generations), 13 subjects with not clearly identifiable state of genetic loading and 27 control subjects from families demonstrating no psychiatric disorder over three generations. All probands were between 18 and 75 years old. All schizophrenic patients were treated with psychotropic drugs. Subjects suffering from dementia, neurological illnesses, severe brain injuries or brain tumors at the time of the examination were excluded from the sample. Demographic statistics divided by diagnostic group of intervening variables like sex, age, education or medication are given in Table 1.

The following standardized examinations were performed on each subject after written informed consent was subscribed: a detailed biographic interview (Bassett et al. 1993) including a test of hand preference (Annett 1970), a psychopathological status (PANSS (Kay et al. 1987), Mini Mental State Examination (MMSE, Folstein et al. 1975), MWT-B (Lehrl 1977)), a consensus diagnosis based on SCID I and II interviews (Wittchen et al. 1991) of two independent psychiatrists, a MRI scan and a blood sample for molecular genetic studies. The mothers of the probands were interviewed in a standardized way to identify developmental risk factors using the Premorbid Adjustment Scale (PAS, Cannon-Spoor et al. 1982) and obstetric complications using the McNeil-Sjöstrom Scale, where pregnancy complications, labor delivery complications and neonatal complications of definite severity were scored (McNeil et al. 1994, Smith et al. 1998). This study was approved by the ethics committees of the Universities of Düsseldorf and Bonn.

MRI scanning

MRI scans taken at the Heinrich-Heine University Düsseldorf were obtained on a Siemens-Magnetom using a 1.5 Tesla superconductive magnet and a circularly polarized head coil. After alignment of the interhemispheric plane with the sagittal view of the brain, a T1-weighted fast gradient echo sequence (fast low angle shot, FLASH, 40 ms repetition time, 5 ms echo time, 40 degree flip angle, 1 excitation, 25 cm field of view, 15 cm thickness of the excited volume) was applied. The resulting data set consisted of 128 consecutive slices with digital images of 1.17 mm thickness and a pixel size of 1 x 1 mm which enabled distinctions between CSF space and brain tissue.

MRI scans at the Friedrich-Wilhelms University Bonn were obtained on a 1.5 Tesla Philips Gyroscan. Sagittal T1-weighted TFE sequences (turbo gradient echo, 12 ms repetition time, 4 ms echo time, 20 degree flip angle, 1 excitation, 25 cm field of view, 16 cm thickness of the excited volume) were applied generating 160 consecutive slices of 1.0 mm thickness.

Since conditions of MRI scanning in Bonn and Düsseldorf were comparable but not identical, site of MRI was used as an independent factor in the statistical analysis as described below.

Processing of the MRI scans

Preprocessing of the MRI scans was done by IDL (Interactive Data Language, Robb and Barillot 1989), a computing environment for the interactive analysis and visualization of data. We used this array-oriented computer language to write some of our own programs to perform the following procedures.

All scans were composed successively to a new 3-D data file containing all brain slices. This data set could be rotated in arbitrary directions. Applying the method of Talairach (Talairach and Tournoux 1988), brains were aligned using the anterior and posterior commissures [(AC) and (PC)] as reference points. The images were converted to byte data with 256 gray tones. The original data files containing 16 bits per pixel were compressed to 8 bit data, permitting accelerated

Table 1 Demographic variables of intervening variables divided by diagnostic group

	Control Subjects			FM no psy. Disorder			FM w. psy. Disorder			FM w. Schizophrenia				
	n	m	sd	n	m	sd	n	m	sd	n	m	sd	F	p
Age at MRI	27	35.52	14.79	40	40.58	15.92	24	40.75	12.96	39	33.36	10.61	2.49	0.063
Duration of illness	–	–	–	–	–	–	–	–	–	39	9.00	9.98	–	–
Age at first onset	–	–	–	–	–	–	–	–	–	39	24.38	9.06	–	–
Height	17	173.88	8.04	40	172.76	9.81	24	173.38	8.90	33	176.73	10.21	1.15	0.33
Weight	17	69.26	8.97	40	74.10	11.90	24	69.21	10.31	34	79.94	11.87	5.68	**0.001**
Mini mental	17	29.35	0.93	38	29.63	0.63	24	29.29	1.33	36	28.67	1.51	4.42	**0.006**
Intelligence (MWT-B)	17	32.12	2.67	39	31.18	3.63	22	30.59	4.00	35	29.86	3.64	1.75	0.16
	# first/# second item			# first/# second item			# first/# second item			# first/# second item			Chi^2	p
Sex (# males/# females)	14/13			23/17			10/14			27/13			4.37	0.22
State of genetic loading (# uniaff./# multiaff.)	–			7/31			6/16			10/27			0.97	0.62
Site of MRI (# Düsseldorf/# Bonn)	10/17			31/9			21/3			29/11			18.46	**0.000**
Education (# primary school/ # higher degree)	4/13			11/29			6/18			11/28			0.18	0.98
Hand preference (# right/# not right)	15/0			37/3			21/3			33/5			2.63	0.45
Psychotropic Drugs (# never/# now or former)	16/1			35/5			14/9			0/39			75.45	**0.000**

n sample size; *m* mean; *sd* standard deviation
Controls control subjects from non-affected families; *FM no psy. Disorder* family members lacking a psychiatric diagnosis; *FM w. psy. Disorder* family members with psychiatric disorder; *FM w. Schizophrenia* family members with Schizophrenia

computation with constant image quality. The output file format was compatible to images which can be opened by Analyze software (Mayo Foundation 1999). For the present measurements coronal cuts of 1 mm thickness were used.

Area measurements

Area measurements were obtained using the Analyze 3.0 software tools. The measurement modules provide facilities for extracting quantitative information from 3D images. Measurements were performed in transverse planes parallel to a plane crossing AC and PC. An auto trace algorithm was applied, which allowed a threshold based segmentation by connecting all pixels within a specified threshold range. A seed pixel was set manually. At the selected pixel a trace around the connected region was drawn automatically. Manual adjustment of the threshold range was used to define the trace at the boundaries of the CSF areas. The shape of the ventricular system can be regarded as continuous. For each structure the cross section increases slice by slice until a maximum is reached, thereafter decreasing. Therefore, a successive algorithm could be applied for each structure of each brain to choose the slice, where the anatomical compartment reached its largest extent. For further analysis, we took this maximal value and, in addition, considered adjacent slices neighboring the maximum value to calculate a mean of three slices. Results of adjacent slices should not differ too much. Therefore, this procedure was suitable to check the validity of single measurements. In addition we measured the total brain area in respective slices. A contour was outlined manually at the border of gray matter to the exterior liquor spaces. Finally, we calculated the quotient of the CSF area of interest divided by the corresponding total brain area as dependent variable (Fig. 1).

Statistical analysis

Statistical analyses were performed with SPSS 10.0 for Windows (Norusis 2000); all tests were two-tailed. Boxplots were examined to help identify extreme values.

The dependent variables were relative CSF areas (VBR, third ventricle, SF, temporal horn, interhemispheric fissure) at their maximum extent. The sum of these areas was calculated as a measurement for the total CSF area. If bilateral measures were available, areas were divided into right and left hemisphere and the asymmetry coefficient, defined as $asym.\text{-}coef. = 2 \cdot (right - left)/(right + left)$ was calculated (Galaburda et al. 1987).

An initial stepwise multiple linear regression analysis ($p_{in} = 0.05$, $p_{out} = 0.10$) with the independent variables age, height, weight, site of MRI (Bonn or Düsseldorf), sex and state of genetic loading (member from families uni- or multiple affected with schizophrenia) was performed. As a measure for the explained variance of the model, adjusted r was calculated.

Since the observations came from families, they could not be considered as independent. Consequently, in the next step, for each dependent variable a mixed model ANOVA (respectively ANCOVA) with random factor family, fixed factor diagnostic group and significant predictors from initial regression analysis as covariates or fixed factors was calculated. Since there were no significant main effects for random factor family, it was removed from the model afterwards.

The results of these preliminary statistics regulated the main analysis. The general linear model procedure (GLM) was calculated separately using a multivariate approach when measurements for both hemispheres were available. The independent factor was diagnostic group (FM with schizophrenia, FM with psychiatric disorder, FM without psychiatric disorder, control subjects). Intervening factors or covariates from initial regression analysis were added to the model. For example, if site of the MRI, sex and age were significant predictors, an ANCOVA (diagnostic group × MRI site × sex; covariate age) would have been performed. Results after adjustment of error probabilities according to the Bonferroni method, intending to reduce error probability of first kind, were added. If significant effects for factor diagnostic group were obtained, subgroup analyses were performed afterwards.

To determine the influence of OC and premorbid adjustment on CSF areas, stepwise linear regression analysis ($p_{in} = 0.05$, $p_{out} = 0.10$) was used again. The influence of all variables that were entered into the model was checked with the correlation calculation or mean comparison.

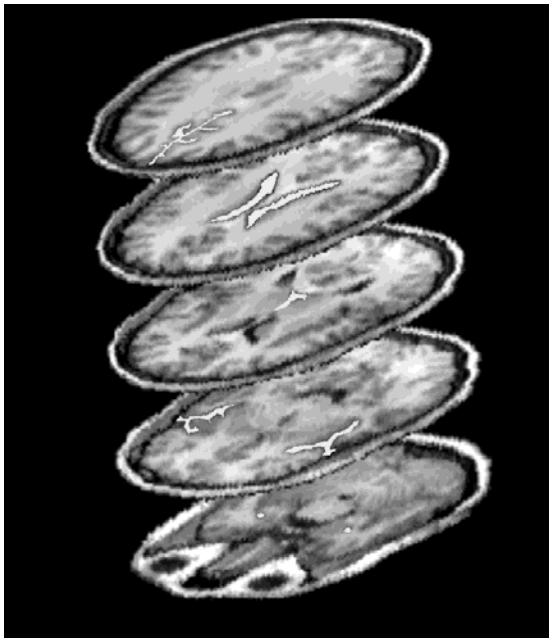


Fig. 1 Outline of examined CSF areas

Reliability

Each of the five raters who did the measurement for one of the CSF areas was blinded for diagnosis. On a selected sample the morphological measurements were performed twice. The reliability was determined using intraclass correlation (ICC, Shrout and Fleiss 1979). For all CSF areas, the intraclass correlation was sufficiently high: SF ($n = 10$, ICC > 0.95), third ventricle ($n = 59$, ICC = 0.92), VBR ($n = 53$, ICC > 0.87) and temporal horn ($n = 135$, ICC > 0.82). Lower reliability was noted for the interhemispheric fissure ($n = 25$, ICC = 0.73). For all corresponding total brain areas, reliability was sufficiently high as well ($n \geq 10$, ICC > 0.95).

Results

Intervening variables

Initial linear stepwise regression analysis indicated an effect of age on all CSF areas ($p < 0.03$). There were positive correlations ($r > 0.26$; $p < 0.003$) between age and all dependent variables, except for the asymmetry coefficients. Site of MRI was a significant predictor of VBR ($p < 0.01$), SF ($p < 0.01$) and interhemispheric fissure ($p = 0.012$) areas. For these landmarks the mean values of the MRI scans obtained at the University of Bonn were between 18 % and 29 % smaller than the MRI scans obtained in Düsseldorf. The asymmetry coefficient of the temporal horn was the predicted by state of genetic loading ($p = 0.013$) as explained more precisely below. There was no significant influence of sex on any of the dependent variables. Explained variances from stepwise regression analysis were relatively low for the temporal horn (adjusted $r < 0.30$) and interhemispheric fissure (adjusted $r = 0.35$), but relatively high for VBR, SF and sum of CSF areas with the predictors age and site of MRI (adjusted $r > 0.54$) and for the third ventricle with the predictor age (adjusted $r = 0.53$).

From univariate mixed model ANOVA/ANCOVA with random factor family, fixed factor diagnostic group and intervening variables mentioned above, there were no significant main effects for factor family, receiving a trend only for the left SF ($F = 1.61$; $p = 0.065$). Consequently, in further analyses the factor family was removed.

Between probands with experience on psychotropic drugs ($n = 54$) and probands without such experience ($n = 65$), there were no significant differences from one-way ANOVA for any of the dependent variables. Likewise, there was no significant influence of the factor hand preference and of intelligence measured by the MWT-B scale.

Diagnostic group effects

Descriptive statistics for all CSF areas separated into control subjects and the three diagnostic subgroups of affected families are summarized in Table 2.

In the GLM analyzing mean differences for diagnostic groups (Table 3), all significant predictor variables from regression analysis were entered for reasons of adjustment. Multivariate analysis showed significant diagnostic effects for the VBR ($F = 2.38$; $p = 0.030$) being confirmed just for the right hemisphere ($F = 3.08$; $p = 0.030$) and for the sum of all CSF areas ($F = 3.09$; $p = 0.006$) where both hemispheres were affected (right: $F = 4.19$; $p = 0.007$; left: $F = 3.15$; $p = 0.028$). Subgroup analysis showed that mean differences were not only visible between schizophrenic patients and control subjects [right VBR (+38 %, $F = 8.39$, $p = 0.005$), right sum of CSF areas (+45 %, $F = 13.75$, $p = 0.001$), left sum of CSF areas (+40 %, $F = 11.46$, $p = 0.001$)], but also between schizophrenic patients and their family members with psychi-

Table 2 Descriptive statistics of CSF areas

Areas[1]	Diagnostic Group											
	Control Subjects			FM no Psy. Disorder			FM w. Psy. Disorder			FM w. Schizophrenia		
	n	m	sd	n	m	sd	n	m	sd	n	m	sd
VBR												
right	27	0.0257	0.0090	40	0.0363	0.0167	24	0.0351	0.0158	40	0.0353	0.0133
left	27	0.0284	0.0078	40	0.0416	0.0199	24	0.0373	0.0141	40	0.0365	0.0118
asym.-coeff.	27	–0.1134	0.1779	40	–0.1199	0.2662	24	–0.1014	0.2244	40	–0.0494	0.2065
Third Ventricle	27	0.0051	0.0019	40	0.0062	0.0031	24	0.0058	0.0027	40	0.0055	0.0018
Sylvian Fissure												
right	17	0.0084	0.0035	40	0.0106	0.0051	24	0.0092	0.0034	40	0.0102	0.0038
left	17	0.0082	0.0030	40	0.0110	0.0053	24	0.0104	0.0041	40	0.0106	0.0036
asym.-coeff.	17	0.0010	0.3303	40	–0.0324	0.2270	24	–0.1241	0.2460	40	–0.0267	0.2474
Temporal Horn												
right	26	0.0022	0.0008	40	0.0027	0.0021	24	0.0027	0.0018	40	0.0024	0.0011
left	26	0.0019	0.0007	40	0.0023	0.0014	24	0.0022	0.0013	40	0.0021	0.0010
asym.-coeff.	26	0.1691	0.4569	40	0.1213	0.3966	24	0.2094	0.3652	40	0.1367	0.3562
Interhemispheric Fissure	26	0.0085	0.0018	40	0.0091	0.0029	24	0.0084	0.0024	39	0.0086	0.0023
Sum of CSF Areas												
right	16	0.0331	0.0071	40	0.050	0.022	24	0.047	0.019	40	0.048	0.014
left	16	0.0352	0.0080	40	0.055	0.025	24	0.050	0.017	40	0.049	0.013
asym.-coeff.	16	–0.0592	0.1397	40	–0.092	0.224	24	–0.084	0.176	40	–0.037	0.155

n group size; *m* mean; *sd* standard deviation; *asym.-coeff.* asymmetry coefficient
FM no Psy. Disorder family members lacking a psychiatric diagnosis; *FM w. Psy. Disorder* family members with psychiatric disorder; *FM w. Schizophrenia* family members with schizophrenia
[1] Ratio CSF area divided by corresponding total brain area at the slice where the structure reaches its maximum

atric disorder [right VBR (F = 5.32, p = 0.025), right sum of CSF areas (F = 7.86, p = 0.007) and left sum of CSF areas (F = 4.21, p = 0.045)], where the enlargement did not exceed 10 %.[1] However, if error probabilities were adjusted according to Bonferroni, just global differences for sum of CSF areas would remain significant.

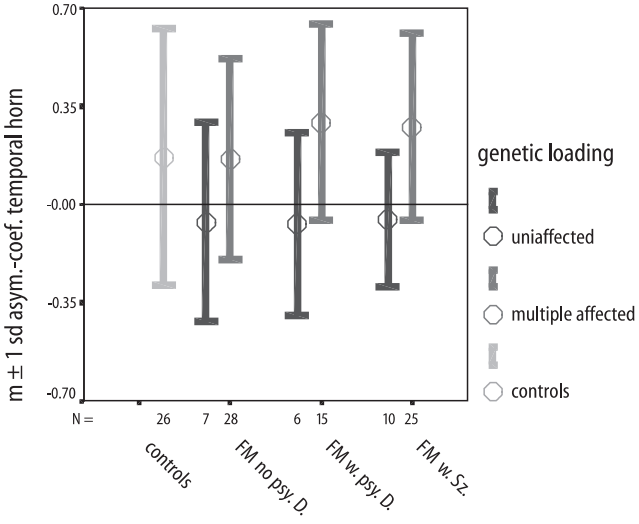
Genetic loading

The state of genetic loading predicted only the temporal horn asymmetry (Fig. 2). While control subjects and all diagnostic subgroups from multiple affected families showed right sided asymmetry (right > left), subjects from uniaffected families were left lateralized, independent of the psychiatric diagnosis (F = 5.60; p = 0.005). Although for the interhemispheric fissure the state of genetic loading was no predictor from stepwise regression analysis, one-way ANOVA showed a significant enlargement for multiple affected compared to uniaffected families (+19 %; F = 3.61, p = 0.030).

Obstetric complications and premorbid adjustment

Neonatal OC predicted the enlargement of lateral ventricles with significantly positive correlations with right (r = 0.36; p = 0.008) and left (r = 0.29; p = 0.032) VBR. Pregnancy and labor delivery complications were no predictors for the selected CSF areas.

Analyzing the PAS data, premorbid motoric disorders showed an influence on left VBR (F = 7.43; p = 0.009) with a ventricular enlargement of 39 % in



ANOVA (factor state of genetic loading): F = 5.60; p = 0.005; *m* mean; *sd* standard deviation; *asym.-coef.* asymmetry coefficient; *controls* control subjects from non-affected families; *FM no psy. D.* family members lacking a psychiatric diagnosis; *FM w. psy. D.* family members with psychiatric disorder; *FM w. Sz.* family members with schizophrenia

Fig. 2 Interaction between brain structure and state of genetic loading

1 Since there were no significant differences between diagnostic groups for SF from multivariate analysis, the enlargement of the right SF in schizophrenic patients compared to their family members with psychiatric disorder (+9 %; F = 7.98; df = 1,58; p = 0.006) should not be interpreted.

Table 3 MANCOVA (Diagnostic Group x Significant Predictors)[1, 2]; subgroup analysis only in case of significance

	Factor Diagnostic Group		Subgroup Analysis between Diagnostic Groups			
	F	p		p	p	p
VBR						
multivariate	2.38	**0.030**		**FM no psy. D.**	**FM w. psy. D.**	**FM w. Sz.**
right	3.08	**0.030**	**Controls**	0.23	0.72	**0.005**
			FM no psy. D.		0.26	0.17
			FM w. psy. D.			**0.025**
			FM w. Sz.			
left	2.14	0.098				
asym.-coeff.	0.78	0.51				
Third Ventricle	0.65	0.59				
Sylvian Fissure						
multivariate	1.64	0.14				
right	3.06	0.031				
left	1.90	0.13				
asym.-coeff.	1.07	0.37				
Temporal Horn						
multivariate	0.30	0.94				
right	0.25	0.86				
left	0.45	0.72				
asym.-coeff.	0.21	0.81				
Interhemispheric Fissure	1.33	0.27				
Sum CSF Areas						
multivariate	3.09	**0.006**		**FM no psy. D.**	**FM w. psy. D.**	**FM w. Sz.**
right	4.19	**0.007**	**Controls**	0.32	0.34	**0.001**
			FM no psy. D.		0.22	0.10
			FM w. psy. D.			**0.007**
			FM w. Sz.			
				FM no psy. D.	**FM w. psy. D.**	**FM w. Sz.**
left	3.15	**0.028**	**Controls**	0.10	0.82	**0.001**
			FM no psy. D.		0.21	0.78
			FM w. psy. D.			**0.045**
			FM w. Sz.			
asym.-coeff.	0.67	0.57				

Controls Control subjects from non affected families; *FM no psy. D.* family members lacking a psychiatric diagnosis; *FM w. psy. D.* family members with psychiatric disorder; *FM w. Sz.* family members with schizophrenia

[1] All significant factors from linear stepwise regression analysis were included as influence factors in the MANCOVA

[2] All significant interval scaled variables from regression analysis were included as covariates in the MANCOVA

probands with motoric disorders. There were positive correlations between sexual contact disorders and the size of the third ventricle ($r = 0.39$; $p = 0.006$), while convulsive attacks had an influence on the SF (right: +58 %; $F = 5.43$; $p = 0.024$; left: + 69 %; $F = 8.22$; $p = 0.006$).

Intercorrelations

For the entire sample, highly significant intercorrelations between all CSF areas ($0.25 < r < 0.65$) were observed. For schizophrenic subjects there were significant intercorrelations between VBR and the third ventricle ($r = 0.33$; $p = 0.038$), VBR and the temporal horn ($r = 0.40$; $p = 0.010$), the interhemispheric fissure and the third ventricle ($r = 0.34$; $p = 0.032$), and interhemispheric fissure and SF ($r = 0.56$; $p < 0.001$).

Discussion

Enlarged VBR is a finding corresponding with other family studies. Significant increases of the VBR in schizophrenics compared to family members without psychiatric disorder but not compared to family members with psychiatric disorder were found by Silverman et al. (1998). Increase of lateral ventricles in schizophrenic patients compared to their relatives was also shown by Zorilla et al. (1997), Cannon et al. (1998) and Sharma et al. (1998); the latter additionally found a volume increase in relatives being obligate gene carriers for schizophrenia. A ventricular enlargement in schizophrenic patients compared to control subjects but not to their siblings was found by Staal et al. (2000).

Honer et al. (1995) found a bilateral enlargement of the SF volume in schizophrenic patients compared to their non-schizophrenic relatives. Falkai et al. (2002) could replicate this finding for schizophrenic subjects from uniaffected and multiple affected families, where

the SF was increased to the same degree compared to healthy family members and genetically independent control subjects. In the present study, SF enlargement was only significant from univariate analysis on the right side. A possible explanation is that area measurements might be not as sensitive as volumetric analysis.

It was interesting to note that an enlargement of almost all CSF areas was detected in schizophrenic patients. Therefore, CSF area enlargement can be interpreted as a sign for diffuse cortical and subcortical atrophy in schizophrenia. After Bonferroni correction the level of significance was reached for the sum of CSF areas only, but respect should also be given to the results without Bonferroni correction, since this method is very conservative, often concealing existing differences.

From subgroup analysis for diagnostic group, CSF areas of schizophrenic patients were increased compared to relatives with psychiatric illnesses other than schizophrenia as well as to control subjects, but not in comparison to healthy family members, who ranged between the other two familial groups. This might be a sample artifact.

The state of genetic loading predicted temporal horn asymmetry independent of the psychiatric diagnosis. Uniaffected families revealed a loss of asymmetry compared to multiple affected as well as control families. This was somewhat unexpected but based on the asymmetry literature in schizophrenia within the mainstream of published data. About 70 % – 90 % of patients included in those studies are from uniaffected families having no family history of psychosis. Since for schizophrenic patients from multiple affected families temporal horn asymmetry was not inverted, this finding is an indication that disturbed asymmetry is influenced by environmental rather than genetic factors.

For the interhemispheric fissure there was a significant enlargement for multiple affected compared to uniaffected families, while the control subjects ranged between these two groups. On other CSF areas, such as VBR or SF, no influence of factor state of genetic loading could be shown. This could also be interpreted as a sign of genetic loading influences on frontal lobe structures in schizophrenia.

These results are in line with Thompson et al. (2001) who found an influence of genetic factors on structural properties in frontal regions, and with Baare et al. (2001) showing that genetic influence on lateral ventricles was of minor importance. Results stand in contrast to Pfefferbaum et al. (2000), considering a genetic influence on lateral ventricle size of nearly 80 % in a study where only elder male twins were analyzed.

Cannon et al. (1989, 1993) found that OC correlated with VBR and third ventricle, but not with SF and interhemispheric fissure especially in probands with high genetic risk. We could partially replicate these findings, whereas other authors failed to find an influence of OC on ventricular size (Jones et al. 1994, Reddy et al. 1990).

It was shown that premorbid adjustment correlates with VBR (Levitt et al. 1994). We could expand this finding to other CSF areas. In a study of Keefe et al. (1989) premorbid sociosexual functioning correlated with ventricular asymmetry. We could not duplicate this result, but found an influence on the third ventricle area.

There are some limitations of this study. First, it can be argued that volumetric analysis might have been more effective than comparing areas. However, the area measurements resulted from a well-defined algorithm that was transferred from the validated VBR concept. A second important shortcoming is the use of the data measured on two different MRI scanners, especially because there were significant differences for factor site of MRI. However, the large sample size allowed us to consider site of MRI as an independent factor. Thus, all analyses were adjusted for scanner effects. A third problem of this study is a trend for age differences between the diagnostic groups; on the other hand, there were significantly positive correlations between age and all CSF areas. For this reason analyses were adjusted for age at MRI by use as a covariate in the GLM, which is an adequate statistical procedure to compensate age effects. In addition, results may be influenced by an overrepresentation of males or females in certain diagnostic groups. For example, in the group of FM with psychiatric disorders, females with depressive diseases predominated. However, this circumstance should not have a large effect on the results, since there were no significant differences for factor sex for any of the dependent variables. Another point that needs to be discussed is the calculation of the sum of all areas as a measure for total CSF. This concept may be criticized since the CSF sum puts a larger weight on the VBR than on all other area. On the other hand, the sum of the CSF areas is a global measure for CSF areas reducing variance relative to its mean compared with each single CSF area and for this reason being more sensitive in detecting differences between the diagnostic groups.

In summary, this study demonstrates that schizophrenic patients reveal generalized CSF enlargement compared to their relatives and control subjects. There are hints for an influence of genetic loading on the enlargement of the temporal horn and interhemispheric fissure.

If these findings are replicable they point to genetic mechanisms in frontal and temporal brain regions while OC exert a diffuse add-on effect leading to structural changes underlying the pathophysiology of schizophrenia.

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