

Brain morphology in antipsychotic-naïve schizophrenia: a study of multiple brain structures*

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Background Although brain volume changes are found in schizophrenia, only a limited number of structural magnetic resonance imaging studies have exclusively examined antipsychotic-naïve patients.

Aims To comprehensively investigate multiple brain structures in a single sample of patients who were antipsychotic-naïve.

Method Twenty antipsychotic-naïve patients with first-episode schizophrenia and 20 healthy comparison subjects were included. Intracranial, total brain, frontal lobe, grey and white matter, cerebellar, hippocampal, parahippocampal, thalamic, caudate nucleus and lateral and third ventricular volumes were measured. Repeated-measures analyses of (co)variance were conducted with intracranial volume as covariate.

Results Third ventricle volume enlargement was found in patients compared with the healthy subjects. No differences were found in other brain regions.

Conclusions These findings suggest that some brain abnormalities are present in the early stages of schizophrenia. Moreover, it suggests that brain abnormalities reported in patients with chronic schizophrenia develop in a later stage of the disease and/or are medication induced.

Declaration of interest None.

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Numerous imaging studies have reported morphological brain abnormalities in schizophrenia, including studies in first-episode schizophrenia (for reviews see McCarley *et al*, 1999; Wright *et al*, 2000). However, it is difficult to establish whether these structural brain abnormalities are caused by the disease or are from the effects of treatment. Imaging studies in patients with schizophrenia who have never been exposed to antipsychotic medication may help to clarify whether brain changes are already present in an early stage of the disease and are independent of medication use. This current study examined multiple brain structures in a single sample of antipsychotic-naïve patients with schizophrenia compared with a sample of carefully matched healthy comparison subjects. Intracranial volume, total brain, grey and white matter of the cerebrum, frontal lobe, cerebellar, hippocampal, parahippocampal, thalamic, caudate nucleus and lateral and third ventricular volumes were assessed.

As evidence is accumulating that medication may alter brain structures (increases in basal ganglia volumes have been related to antipsychotic intake (Chakos *et al*, 1994; Keshavan *et al*, 1994; Scheepers *et al*, 2001) and decreases in frontal lobe volume have been related to the amount of antipsychotic medication used (Gur *et al*, 1998a; Madsen *et al*, 1998)), the study of brain morphology in antipsychotic-naïve patients with schizophrenia is crucial for an understanding of the disease. Studies comparing antipsychotic-naïve patients with first-episode schizophrenia with healthy comparison subjects have examined only one or a few brain structures (Table 1). These studies have inconsistently reported brain volume changes in antipsychotic-naïve patients with schizophrenia compared with healthy volunteers, which could be caused by factors such as a large variation in scanning acquisition and volumetric measures, inclusion of small numbers of subjects, inclusion of patients

with a diagnosis other than schizophrenia and failure to match for age, gender, socio-economic class or handedness. In addition, some studies were not designed to exclusively compare antipsychotic-naïve patients with healthy comparison subjects.

METHOD

Subjects

Twenty patients in their first psychotic episode of schizophrenia were recruited from the First-Episode Schizophrenia Research programme at the University Medical Centre Utrecht. Patients had not received antipsychotic treatment prior to scanning. All patients met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia (11 paranoid, 8 undifferentiated, 1 disorganised type), on the basis of the Comprehensive Assessment of Symptoms and History (CASH; Andreasen & Arndt, 1992) rated by two independent raters. Nineteen patients (one patient was lost to follow-up) had the diagnosis confirmed after 1 year. The start of prodromal symptoms and psychotic illness was measured by a shortened version of the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Häfner *et al*, 1992). Severity of illness was measured with the Positive and Negative Symptom Scale (PANSS; Kay *et al*, 1987). Twenty healthy comparison subjects were recruited and carefully matched for gender, age, parental education and handedness. They were all screened with the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-L; Endicott & Spitzer, 1978) and fulfilled criteria for ‘never mentally ill’. All subjects were physically healthy (except one patient who had congenital hypothyroidism, but was stable on supplementation medication), had neither a history of head injury nor a diagnosis of drug or alcohol misuse or dependence. All patients and healthy comparison subjects provided written informed consent to participate in the study. For demographic and clinical data see Table 2.

Brain imaging

MRI acquisition

Magnetic resonance images (MRIs) were acquired on a Philips NT scanner operating at 1.5 T. A T1-weighted three-dimensional fast field echo (3D-FFE; echo time (TE)=4.6 ms, repetition time (TR)=30 ms, flip angle=30°, field of view

Table 1 Review of magnetic resonance imaging (MRI) literature in antipsychotic-naive patients with schizophrenia

Author	Subjects	Brain regions examined	Matching	MRI	Results	Comment
Buchsbaum <i>et al.</i> , 1996	20 m-sz 15 nc	Thalamus	Not clearly matched	7.5-mm slices	No volume differences	Primarily PET study
Keshavan <i>et al.</i> , 1998a	16 m-sz 9 non sz 17 nc	Cranium, caudate, putamen	Age, gender, parental education and own education	1.5 T 2.8-mm slices	Left caudate reduced in both patient groups	
Keshavan <i>et al.</i> , 1998b	17 m-sz 8 non sz 17 nc	Cranium, STG, cerebellum	Not clearly matched	1.5 T 5-mm slices 1-mm gap	Smaller left STG	After 1 year follow-up repeat MRI showed reduced total STG
Gur <i>et al.</i> , 1998a ¹	20 m-sz 20 prev. treat. sz 17 nc	Total brain, CSF, frontal lobe, temporal lobe	Not clearly matched	1.5 T 5-mm slices	Reduced total brain, frontal and temporal lobes. CSF no difference	Designed as a follow-up study
Gur <i>et al.</i> , 1998b	21 m-sz 75 prev. treat. sz 128 nc	Cranium, caudate, putamen, globus pallidus, thalamus, total brain, CSF, ventricles	Age, parental education, handedness	1.5 T 1-mm slices	Thalamic volume reduction trend. Total brain, CSF, ventricles, globus pallidus, putamen no difference	Increased subcortical volumes related to amount of antipsychotics
Shihabuddin <i>et al.</i> , 1998	7 m-sz 11 drug-free sz 24 nc	Caudate, putamen	Age, gender	1.2-mm slices	Smaller caudate and putamen	Primarily PET study
Westmoreland <i>et al.</i> , 1999	36 m-sz 43 nc	Cranium, grey and white matter, caudate, CSF	Age, gender, socio-economic status	1.5 T 1.5-mm slices	Smaller caudate. Differences of cranium, grey and white matter and CSF not reported	Corrected for intracranial volume (calculated by adding grey, white matter and CSF)
Gur <i>et al.</i> , 2000a ¹	39 m-sz 61 prev. treat. sz 110 nc	Hippocampus, amygdala, STG, temporal pole	Parental education	1.5 T 1-mm slices	Smaller hippocampus, STG and temporal pole. Amygdala no difference	
Gur <i>et al.</i> , 2000b ¹	29 m-sz 41 prev. treat. sz 81 nc	Prefrontal white and grey matter (orbital and dorsal regions)	Parental education	1.5 T 1-mm slices	Reduced prefrontal grey matter	
Laakso <i>et al.</i> , 2001	18 m-sz 22 nc	Hippocampus	Age, gender, handedness, parental socio-economic status	1.5 T 1.5-mm slices	No difference in hippocampal volume	
Ichimiya <i>et al.</i> , 2001	20 m-sz 20 nc	Cranium, cerebellum, cerebellar grey and white, vermis	Age?, handedness	1.5 T 2-mm slices	Reduced cerebellar vermis. Total cerebellum, cranium and cerebellum no difference	

m-sz, antipsychotic-naive patients with schizophrenia; non sz, patients with other psychotic disorders; prev. treat. sz, previously treated patients with schizophrenia; nc, normal controls; STG, superior temporal gyrus; CSF, cerebrospinal fluid; PET, positron emission tomography; T, tesla.
1. Combined analysis on m- and previously treated patients. Post hoc analysis m-sz were no different from prev. treated patients.

(FOV)=256/80% mm) with 160–180 contiguous coronal 1.2-mm slices, and a T2-weighted dual echo turbo spin-echo (DTSE: TE1=14 ms, TE2=80 ms, TR=6350 ms, flip angle=90°, FOV=256/80% mm) with 120 contiguous coronal 1.6-mm slices of the whole head were used for the quantitative measurements. In addition, a T2-weighted DTSE (TE1=9 ms, TE2=100 ms, TR=2200 ms, flip angle=90°, FOV=250/100% mm) with 17 axial 5-mm slices and 1.2-mm gap of the whole head was acquired for clinical neurodiagnostic evaluation. Processing was carried out on the neuroimaging computer network of the Department of Psychiatry. Before quantitative assessments, 10 images were randomly chosen and cloned for interrater reliability purposes determined by the intraclass correlation coefficient (ICC). All images were coded to ensure blindness for subject identification and diagnosis, scans were entered into Talairach frame (no scaling) (Talairach & Tournoux, 1988) and corrected for inhomogeneities in the magnetic field (Sled *et al*, 1998).

Volume measurements

Intracranial, total brain, cerebral grey and white matter, lateral ventricles and third ventricle and cerebellar volumes were measured automatically by using histogram analysis algorithms and series of mathematical morphological operators to connect all voxels of interest (Schnack *et al*, 2001a,b). Intracranial volume was segmented on the DTSE scans, with the foramen magnum being used as inferior boundary. Total brain volumes were segmented on the 3D-FEE (T1-weighted) scans and contained grey and white matter tissue only. In lateral ventricle segmentation automatic decision rules bridged connections not detectable and prevented 'leaking' into cisterns. The third ventricle was limited by coronal slices, clearly showing the anterior and posterior commissures; the upper boundary was a plane through the plexus choroideus ventriculi tertii in the midsagittal slice perpendicular to this slice. The cerebellum was limited by the tentorium cerebelli and the brain-stem. All images were checked after the measurements and corrected manually if necessary. The interrater reliability of the measurements determined by the ICC based on 10 brains was 0.95 and higher. Segmentation of the frontal lobe was performed automatically using

Table 2 Demographic and clinical data for antipsychotic-naïve patients with schizophrenia and healthy comparison subjects

	Patients (n=20)	Controls (n=20)	t or χ^2	P
Gender, n				
Male	16	16	$\chi^2=0.00$	1.00
Female	4	4		
Handedness, n				
Right	18	18	$\chi^2=0.00$	1.00
Left	2	2		
Age, years (mean (s.d.))	27.63 (6.43)	27.24 (6.30)	t=0.20	0.85
Weight, kg (mean (s.d.))	75.50 (14.64)	77.05 (11.68)	t=0.37	0.72
Height, cm (mean (s.d.))	175.45 (9.43)	184.68 (7.94)	t=3.30	0.002*
Parental education level, years (mean (s.d.))	12.3 (3.8)	14.1 (2.7)	t=1.18	0.11
Education, years (mean (s.d.))	11.6 (3.0)	12.7 (3.0)	t=1.67	0.25
Subtype of schizophrenia according to DSM-IV, n				
Paranoid	11			
Disorganised	1			
Undifferentiated	8			
Prodromal phase, months (mean (s.d.))	48.1 (61.1)			
Psychosis, months (mean (s.d.))	17.5 (27.2)			
PANSS positive symptoms (mean (s.d.))	21.1 (5.1)			
PANSS negative symptoms (mean (s.d.))	21.3 (6.3)			
PANSS psychopathology (mean (s.d.))	38.0 (11.1)			

PANSS, Positive and Negative Symptom Scale. *P ≤ 0.05.

the ANIMAL anatomical segmentation algorithm (Collins *et al*, 1994), which was validated previously for frontal lobe volume measurements (Mandl *et al*, 1999).

Quantitative measurements of the caudate nucleus, thalamus, hippocampus and parahippocampus were obtained manually, from the 3D-FEE image using Analyze™ (Robb, 1995). The caudate nucleus was anteriorly defined in the first slice in which it was clearly visible. Its medial border was the lateral ventricle. Laterally, it was limited by the internal capsule, excluding the interconnecting grey matter striae between caudate and putamen visible in the internal capsule; posteriorly, by the last slice before the one in which the posterior commissure was clearly visible. Its inferior border was defined: anteriorly by the white matter connecting the rostrum corporis callosi and the capsula externa. Then, from the first slice where the putamen is clearly visible until the slice anterior to the slice in which the anterior commissure crosses the midline, the nucleus accumbens was separated by a line from the most inferior point of the lateral ventricle to the most

inferior point of the internal capsule (adapted from Chakos *et al*, 1994). The thalamus was anteriorly defined in the first slice in which it was clearly visible, and precisely demarcated in the subsequent slices until the first slice after the coronal slice that included the posterior commissure. Its lateral border was defined by the internal capsule; its medial border by the third ventricle and its inferior boundary was defined by the anterior commissure–posterior commissure plane. Segmentation of the hippocampus was started in the coronal slice in which the mammillary bodies were visible and stopped when the fornix was visible as a continuous tract (adapted from Watson *et al*, 1992). Parahippocampal gyrus segmentation began in the coronal slice in which the optic tract is situated above the amygdala. The posterior commissure was its posterior border. Single operators performed the volume measurements of the above-named structures. The ICC for the left and right caudate nucleus was 0.98 and 0.99, for the thalamus, 0.77 and 0.86, for the hippocampus, 0.81 and 0.80 and for the parahippocampal gyrus, 0.77 and 0.75.

Statistical analyses

Repeated-measures analysis of covariance was conducted for total brain, grey and white matter of the cerebrum (total brain, excluding cerebellum and brainstem), frontal lobe, cerebellum, hippocampus, parahippocampus, thalamus, caudate volumes and ventricles, with group (patients, healthy comparison subjects) as the between-subjects variable and, if applicable, side (left, right) and matter (grey, white) as the within-subjects variable. Intracranial brain volume served as covariate for total brain, grey and white matter of the cerebrum, cerebellar, lateral and third ventricle volume measures. Total brain volume served as covariant for frontal lobe, hippocampal, parahippocampal, thalamic and caudate volumes.

To examine associations between significant brain volume differences and clinical variables (prodromal phase, duration of untreated psychosis, PANSS scores) Pearson's correlations were calculated with intracranial volume as a covariate. To assess the power of the study a power analysis, uncorrected for intracranial volume, was carried out with a probability of 0.7 at an α level of 0.05.

RESULTS

As seen in Table 2, patients and healthy comparison subjects did not significantly differ for gender, handedness, age, weight and parental education. Although not matched for education, patients did not differ from healthy comparison subjects on years of education. Patients and healthy comparison subjects did significantly differ in height, but as intracranial volume was used as covariate, the results presented below are uncontrolled for height. However, results did not change when height was used as a covariate.

Mean (s.d.) volumes of total brain, frontal brain, grey matter, white matter, cerebellum, hippocampus, parahippocampus, thalamus, caudate nucleus, lateral ventricles and third ventricle are presented in Table 3 for patients and healthy comparison subjects.

Intracranial volume and total brain measures

Intracranial volume ($F=2.59$, $d.f.=1,38$, $P=0.12$), total brain volume ($F=0.55$, $d.f.=1,37$, $P=0.47$) and cerebral volume

Table 3 Volumes (cm^3) of brain regions in antipsychotic-naive patients with schizophrenia and comparison subjects

Region	Patients with schizophrenia ($n=20$)	Comparison subjects ($n=20$)	Effect size	Observed power
Cranium	1463.25 (130.71)	1538.87 (164.37)	0.06	0.35
Total brain	1281.57 (118.70)	1353.94 (138.96)	0.08	0.41
Grey matter	669.87 (58.66)	691.93 (54.92)	0.04	0.22
White matter	455.19 (66.27)	499.47 (90.85)	0.08	0.40
Frontal lobe	280.99 (30.69)	299.64 (32.39)	0.08	0.45
Cerebellum	142.78 (14.71)	148.52 (13.03)	0.04	0.25
Caudate	9.22 (1.08)	9.19 (1.24)	0.00	0.05
Thalamus	14.37 (1.31)	14.97 (2.09)	0.03	0.18
Hippocampus	8.01 (0.77)	8.36 (0.80)	0.05	0.28
Parahippocampus	4.93 (0.94)	5.63 (1.14)	0.11	0.55
Lateral ventricles	13.18 (6.90)	14.82 (12.21)	0.01	0.08
Third ventricle*	0.85 (0.32)	0.62 (0.36)	0.11	0.54

Values are mean (s.d.). Effect size measured by the eta-squared based on the raw data.
* $P \leq 0.05$.

($F=0.36$, $d.f.=1,37$, $P=0.56$) did not differ significantly between the two groups, nor was there a significant interaction effect of group with matter (grey, white) of the cerebrum ($F=0.21$, $d.f.=1,38$, $P=0.65$).

Frontal lobe and cerebellum

Frontal lobe volume ($F=0.34$, $d.f.=1,37$, $P=0.56$) and cerebellar volume ($F=0.34$, $d.f.=1,37$, $P=0.57$) did not differ significantly between the two groups.

Hippocampus, parahippocampus, thalamus and caudate nucleus

Hippocampus ($F=0.11$, $d.f.=1,37$, $P=0.74$), parahippocampus ($F=2.05$, $d.f.=1,37$, $P=0.16$), thalamus ($F=0.28$, $d.f.=1,37$, $P=0.60$), and caudate nucleus ($F=1.23$, $d.f.=1,37$, $P=0.27$) did not differ significantly between the two groups.

Ventricles

Lateral ventricle volume ($F=0.15$, $d.f.=1,37$, $P=0.70$) did not significantly differ between the two groups. However, third ventricle volume was significantly larger in patients compared with the comparison subjects ($F=8.92$, $d.f.=1,37$, $P=0.005$) (Fig.1).

No significant interaction effects of group with matter or with side for any of

these measures were found. No correlations were found between third ventricle volume and the clinical data. Excluding the patient with congenital hypothyroidism and her matched comparison subject did not alter the results.

DISCUSSION

This study compared multiple brain structures in a sample of antipsychotic-naïve patients with schizophrenia with those of matched healthy comparison subjects. Volumes of the cranium, total brain, grey and white matter of the cerebrum, frontal lobe, cerebellum, hippocampus, parahippocampus, thalamus, caudate nucleus and lateral and third ventricles were measured. We found third ventricle enlargement in the patients. The other structures were similar in both patients with schizophrenia and healthy comparison subjects.

Third ventricle enlargement in antipsychotic-naïve patients with schizophrenia

To our knowledge, third ventricle volume has not been examined with MRI in patients with schizophrenia who were antipsychotic-naïve. Third ventricle enlargement has been reported in studies of first-episode schizophrenia examining mixed (antipsychotic-naïve and -treated subjects) samples of patients (for review

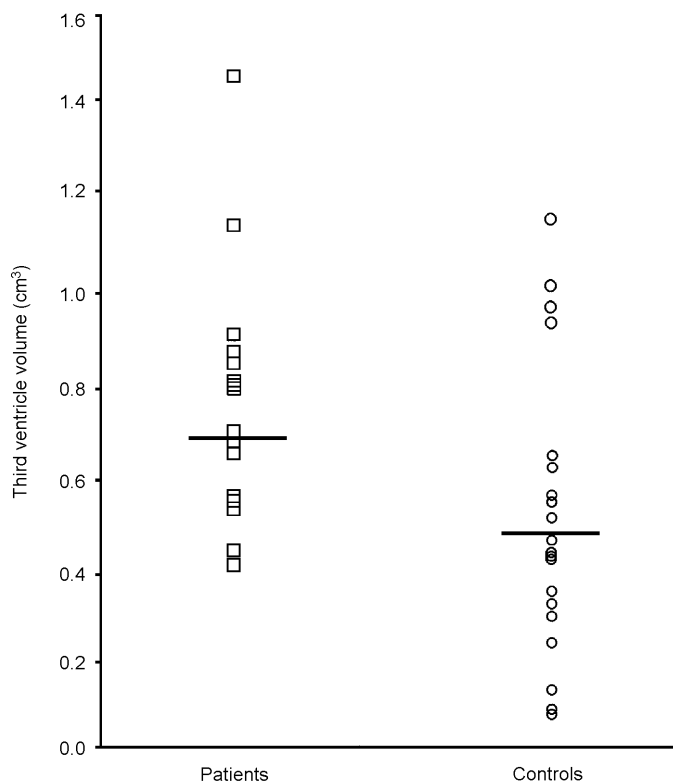


Fig. 1 Third ventricle volume in antipsychotic-naïve patients with first-episode schizophrenia and healthy comparison subjects. — indicates mean third ventricle volume for the patients and controls.

see Fannon *et al*, 2000). A possible volume reduction in surrounding diencephalic brain regions could explain the third ventricle enlargement, although in our study this was not expressed in a reduction of thalamic volume. The absence of a reduction in thalamic volume in our study is consistent with the studies performed in antipsychotic-naïve patients with schizophrenia (Buchsbau *et al*, 1996; Gur *et al*, 1998b). Interestingly, third ventricle enlargement but also thalamic volume decrease were found in the healthy siblings of patients with schizophrenia (Staal *et al*, 1998, 1999a; Lawrie *et al*, 1999; Seidman *et al*, 1999), suggesting that these findings could be related to a genetic vulnerability for schizophrenia. The discrepancy of an increase of third ventricle without a corresponding decrease in thalamic volume in this study might be related to the relatively limited number of patients included, or could imply that other regions in the proximity of the third ventricle, such as the hypothalamus, are involved. Abnormalities in the hypothalamic–pituitary–adrenal axis have been suggested to be present in schizophrenia (Tandon *et al*, 1991; Jansen *et al*, 2000; Walder *et al*, 2000); however, to date

no study has been published measuring the hypothalamus in schizophrenia.

No volume changes in brain tissue

This study found normal total brain and frontal lobe volume in antipsychotic-naïve patients. This finding is inconsistent with the findings by Gur *et al* (1998a, 2000b), demonstrating total brain and frontal lobe reduction, specifically in prefrontal grey matter, in antipsychotic-naïve patients with schizophrenia. In these studies, however, a mixed sample of antipsychotic-naïve patients and previously treated patients with schizophrenia was examined. Our finding of a normal hippocampus in antipsychotic-naïve patients is congruent with the only other MRI study (Laakso *et al*, 2001) designed to examine hippocampal volumes in antipsychotic-naïve patients compared with healthy comparison subjects. Similar caudate nucleus volumes in both antipsychotic-naïve patients and healthy comparison subjects have also been reported in one study (Gur *et al*, 1998b), but not in others (Keshavan *et al*, 1998a; Shihabuddin *et al*, 1998; Corson *et al*, 1999). The latter studies found

reduced volumes in patients. Differences in the various samples, such as diagnosis and handedness, as well as variations in quantitative assessment techniques might explain these inconsistencies.

Relative paucity of brain abnormalities

The relative paucity of brain abnormalities found in this study may actually be the most striking finding. It stands in marked contrast with findings in patients with more chronic schizophrenia, where volume reductions in total brain and medial temporal lobe structures as well as volume enlargement of lateral ventricles have been reported consistently (for review see Wright *et al*, 2000). However, the most likely reason for this relative paucity of brain abnormalities is a lack of power, as only 20 patients and 20 healthy comparison subjects were included in this study. Several other explanations, besides the lack of power, can be suggested to explain this discrepancy. First, progression of the illness could lead to an increase of brain abnormalities. A limited number of longitudinal studies in patients with first-episode schizophrenia have been conducted suggesting that brain abnormalities may indeed become more prominent over time (DeLisi *et al*, 1997; Gur *et al*, 1998a) at least in a subgroup of patients with poor outcome (Lieberman *et al*, 2001). Second, medication might increase brain abnormalities and could contribute to these brain volume changes as suggested by Gur *et al* (1998a) and Madsen *et al* (1998). Third, finding few brain abnormalities in antipsychotic-naïve patients could be the result of a selection bias favouring the inclusion of patients who have a less severe form of schizophrenia. Two characteristics of our sample, high education and a later age of onset, suggest it might indeed not be representative of all patients with first-episode schizophrenia. In our study no difference between patients and healthy comparison subjects on years of education existed. A total of 9 patients of 20 had even completed part or all of university training. In addition, their mean age at onset was at about 27 years. Interestingly, high education and a later age of onset are both related to good outcome (Johnstone *et al*, 1989; Weiselgren & Lindstrom, 1996), which in turn appears to be associated with a relative lack of brain abnormalities at presentation of illness (Staal *et al*, 1999b). It has also been

suggested that grey matter volume is related to IQ (Andreasen *et al.*, 1993). Therefore, in this study a level of education (and presumably premorbid IQ) similar in patients to that of the healthy comparison subjects could have resulted in finding no decrements in (regional) grey matter volume. Thus, although the relative paucity of brain volume abnormalities in our sample could be indicative of progressive brain changes in schizophrenia because of illness and/or medication, alternatively it could have been the result of a selection bias that may be hard to avoid when studying antipsychotic-naïve patients with schizophrenia.

Future studies

Although it may be practically impossible to determine whether brain abnormalities in schizophrenia result from the progression of the illness and/or medication, the suggestion of medication having an effect on brain volume changes should be an incentive for future longitudinal studies to carefully monitor medication intake.

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CLINICAL IMPLICATIONS

- Third ventricle enlargement in antipsychotic-naïve first-episode patients with schizophrenia suggests abnormalities in schizophrenia in the diencephalic region of the brain at the onset of the disease.
- Antipsychotic medication might be partly implicated for brain abnormalities found in schizophrenia.
- The relative paucity of brain abnormalities in patients with first-episode schizophrenia suggests that an underlying neurodegenerative process cannot be excluded.

LIMITATIONS

- The study group was relatively small as a result of the inclusion requirements such as no prior antipsychotic use and no illicit drug or alcohol misuse/dependence, which is highly prevalent in first-episode schizophrenia.
- Although previous education in patients suggested a high (premorbid) IQ, no formal IQ testing was performed.
- Patients were carefully matched to the healthy comparison subjects but they did significantly differ in height. However, when height was used as a covariate results did not change.

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