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Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study

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Abstract

Gray matter brain volume decreases have been found in patients with schizophrenia as compared to healthy control subjects measured by using Magnetic Resonance Imaging (MRI). An association has been suggested between decreased gray matter volume and poor outcome in chronically ill patients with schizophrenia. The present longitudinal multi-center study investigated whether gray matter volume at illness onset can predict poor outcome in recent-onset schizophrenia after a follow-up of approximately 2 years. An MRI calibration study was performed since scans of patients with recent-onset psychosis were conducted at three sites with 1.5 T MR scanners from two different manufacturers. Applying a linear scaling procedure on the histogram improved comparability between volume measurements acquired from images from the different scanners.

Brain scans were obtained from 109 patients with recent-onset schizophrenia. Volumes of intracranium, total brain, cerebral gray and white matter, third and lateral ventricles, and cerebellum were measured. After a mean follow-up period of approximately 2 years, measurements of symptoms, functioning, need for care, and illness history variables were assessed. No significant correlations were found between the brain volume measures and any of these measures. Gray matter volume at illness onset does not predict outcome after 2 years in recent-onset schizophrenia.

Keywords: Schizophrenia; Recent-onset; Morphology; Gray matter; Multi-center; Calibration

1. Introduction

Brain imaging studies have consistently demonstrated brain volume abnormalities in patients with schizophrenia. In a meta-analysis of Magnetic Resonance Imaging (MRI) studies, the mean cerebral volume of patients was found to be smaller, whereas their mean lateral ventricle volume was increased as compared to healthy control subjects. The loss of total brain volume in patients could mostly be attributed to a decreased gray matter volume (Wright et al., 2000).

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One of the characteristic features of schizophrenia is its heterogeneous course (Schultz and Andreasen, 1999; Wiersma et al., 1998) with a tendency to clinical deterioration and poor clinical outcome (Lieberman, 1999). If structural brain abnormalities of schizophrenia relate to the illness process, one would expect functional status to be related to brain abnormalities.

Cross-sectional studies reported a relationship between structural brain measurements (quantitative and qualitative) and outcome (Davis et al., 1998; Staal et al., 2001; Rossi et al., 2000; Galderisi et al., 2000) by comparing chronically ill patients with either a good or a poor outcome. In these studies, different definitions of poor outcome were used: more than 5 years of complete dependence on others for life necessities and care, lack of employment, and sustained symptomatology (Davis et al., 1998), the total score of the Strauss-Carpenter Outcome Scale (Rossi et al., 2000; Galderisi et al., 2000), and hospitalization for more than 50% of their total duration of illness and continuous hospitalization over the past 3 years (Staal et al., 2001). Despite different outcome definitions, these studies found an association between increased ventricle volume and poor outcome. Moreover, Staal et al. (2001) found decreased gray matter volume in the frontal lobe in patients with poor outcome as compared to patients with good outcome and healthy control subjects.

However, surprisingly few studies have prospectively looked at brain volume measurements (more specifically, increased lateral ventricles, and decreased gray matter volume) and outcome (Wassink et al., 1999; DeLisi et al., 1992, 1998; Van Os et al., 1995) in patients with recent-onset schizophrenia (see Table 1).

In patients experiencing their first psychosis, smaller cerebellum (Wassink et al., 1999), smaller Sylvian fissure (Van Os et al., 1995), larger third ventricle (Van Os et al., 1995), and larger lateral ventricles (DeLisi et al., 1992) were found as predictors of various outcome measures. None of these studies reported information on gray matter volume.

The present longitudinal multi-center study investigated whether gray matter volume at illness onset can predict outcome in recent-onset schizophrenia after a follow-up of approximately 2 years.

2. Methods

This multi-center study of recent-onset schizophrenia and related psychotic disorders focussed on the predictive value of neuropsychological variables and brain volumes measured by using MRI on functional status after a 1- to 2-year follow-up. The neuropsychological data will be presented elsewhere. It was carried out in the Departments of Psychiatry of the university hospitals of Amsterdam, Groningen, and Utrecht and included patients referred to these Departments of Psychiatry for in- or outpatient treatment. Over a period of about 1.5 years (1997–1998), 141

Table 1
Review of literature on prediction of outcome and pharmacological treatment response from MRI brain volume measurements

Reference	Subjects	Measures	Relationship between brain volume and outcome
DeLisi et al., 1992	$N=30$ schizophrenia spectrum recent-onset	volumetric MRI outcome retrospectively, at 2 years	Positive association between lateral ventricles and number of hospitalizations, duration of hospitalization and BPRS
DeLisi et al., 1998	$N=50$ schizophrenia spectrum recent-onset	volumetric MRI outcome prospectively, for 4–5 years	No association between MRI volume measures and outcome
Van Os et al., 1995	$N=140$ functional psychoses	volumetric CT outcome retrospectively, at 4 years	Sylvian fissure volume and third ventricle volume predict negative symptoms and unemployment, the latter is mediated by poor cognitive functioning
Wassink et al., 1999	$N=63$ schizophrenia spectrum recent-onset	volumetric MRI outcome prospectively, for 7 years	Negative association between cerebellar volume and negative and psychotic symptom duration and psychosocial impairment

patients were included in the study: 46 in Amsterdam, 42 in Groningen, and 53 in Utrecht.

2.1. Subjects

In this MRI study, 109 patients (Amsterdam: 25 males/4 females; Groningen: 15/12; Utrecht: 44/9) with recent-onset schizophrenia were included who experienced a first ($n=89$) or second ($n=20$) psychotic episode. Exclusion criteria were mental retardation and a known systemic or neurological illness.

At inclusion, an MRI scan was made. Also, demographic variables, diagnosis, variables of illness history, social functioning, and symptoms were assessed. After a mean follow-up period of 1.8 years (sd = 0.5), these variables were assessed again. Several outcome measures were defined, i.e., (1) time spent in the hospital between inclusion and follow-up, (2) negative symptoms, and (3) social functioning. In addition, (4) need for care in daily functioning was measured. The mean follow-up period of 1.8 years will be referred to as a follow-up period of 2 years throughout the paper.

2.2. Diagnostic assessment and illness history information

After written informed consent, all patients were assessed by means of the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) (CASH; $N=82$) or the Schedules for Clinical Assessment in Neuropsychiatry-section psychosis (Wing et al., 1990) (SCAN; $N=27$) and the substance abuse subscale of the Composite International Diagnostic Interview (Smitten et al., 1998) (CIDI). DSM-IV diagnoses of schizophrenia or related psychotic disorder and/or substance abuse or dependence were based on the results of these interviews. Two independent raters assessed the CASH and SCAN, and diagnostic consensus was achieved in the presence of a psychiatrist. To allow predictions to be made in a representative group of patients, patients who were dependent on or abusing drugs were not excluded from the study. Since information on drug abuse and dependency was acquired prospectively, it was not possible to determine the amount of drug intake reliable. After almost 2 years, diagnosis and drug use were assessed again.

Both at inclusion and follow-up, sociodemographic data, and treatment and illness history were recorded in a modified version of the Interview for the Retrospective Assessment of the Onset of Schizophrenia (Hafner et al., 1992) (IRAOS). The following variables of illness course were defined: duration of untreated psychosis, duration of hospitalization before inclusion (months), and duration of hospitalization since inclusion (months).

Cumulative typical and atypical antipsychotic medication in haloperidol equivalents was available for 79 patients at both inclusion and follow-up. Patients were prescribed typical ($n=8$) and atypical antipsychotics ($n=43$), but a number of patients ($n=26$) were prescribed typical as well as atypical antipsychotics, although not simultaneously, at various times during the follow-up period. Therefore, total cumulative medication was defined as the sum of typical and atypical antipsychotic medication in haloperidol equivalents. Demographic variables, diagnoses, information on drug abuse or dependence, and variables of illness history at inclusion and follow-up are described in Table 2.

2.3. Clinical measurements

Psychopathology was measured, both at inclusion and follow-up, with the Positive and Negative Syndrome Scale (Kay et al., 1987) (PANSS) and the Montgomery Åsberg Depression Rating Scale (Montgomery and Asberg, 1979) (MADRS). From the PANSS, five dimensions were composed: a positive dimension, a negative dimension, depression, agitation-excitement, and disorganization (Wolthaus et al., 2000). The MADRS assesses 10 symptoms of depression on a seven-point scale (0 = absent and 6 = extreme). The total score consists of the sum of all 10 items. Social disability was assessed both at inclusion and follow-up with the Groningen Social Disabilities Schedule (Wiersma et al., 1988) (GSDS). The GSDS consists of eight social roles that are rated on a four-point scale ranging from no disability (0) to severe disability (3). The total score consists of the sum scores of all relevant social roles divided by the number of social roles.

Assessment of need for care in daily functioning was measured only at follow-up, using the Camberwell Assessment of Need (Phelan et al., 1995) (CAN).

Table 2
Demographic information, information on diagnoses, illness history variables, and measures of symptoms, outcome, and brain volumes

Demographic information	At inclusion		At follow-up	
	$N = 109$[a]		$N = 109$[a]	
Included male/female	84/25			
Handedness (right/left/ambidexter/unknown)	86/19/2/2			
	Mean	sd	Mean	sd
Age (years)	24.0	5.8	25.8	5.8
Level of education at inclusion (years)	9.5	2.7		
Parental level of education (years)	11.8	3.9		
Diagnosis (DSM-IV)	*N*		*N*	
295.1 disorganized type	3		5	
295.2 catatonic type	0		1	
295.3 paranoid type	43		53	
295.4 schizophreniform disorder	16		7	
295.6 residual type	4		3	
295.7 schizoaffective disorder	9		11	
295.9 undifferentiated type	23		22	
296.3 depressive disorder	0		1	
296.8 bipolar disorder	0		1	
297.1 delusional disorder	1		1	
298.8 brief psychotic disorder	2		1	
298.9 psychotic Disorder NOS	8		3	
Drug abuse or dependence	63		14	
Illness information	Mean	sd	Mean	sd
Age at first symptoms (years)	21.2	4.6		
Age at first psychotic episode (years)	22.3	5.4		
Age at first medication (years)	22.6	5.5		
Duration of untreated psychosis (months)	4.2	6.1		
Duration of illness since first symptoms (months)	24.9	27.9		
Total duration of hospitalization (months)	3.9	4.9	3.7	5.4
Amount of typical medication (cumulative)[b,c]	689.5 ($n = 18$)	840.5	1086.7 ($n = 8$)	871.9
Amount of atypical medication (cumulative)	1443.0 ($n = 20$)	1693.8	3861.0 ($n = 43$)	2329.1
Amount of both types of medication (cumulative)				
Typical	822.4 ($n = 28$)	817.1	1010.1 ($n = 26$)	1188.1
Atypical	909.9 ($n = 28$)	880.0	4238.0 ($n = 26$)	2412.3
Symptom measures				
PANSS positive	17.7	7.5	15.7	7.4
PANSS negative	15.7	6.1	13.8	6.7
PANSS depression	9.4	3.7	7.8	3.6
PANSS agitation/excitement	6.1	2.4	5.7	3.2
PANSS disorganisation	14.1	5.3	12.8	5.4
MADRS	14.2	10.3	9.5	7.7
Outcome measures				
Social functioning (GSDS)	1.2	0.7	0.8	0.7
Need for care in daily functioning (CAN): patient			0.2	0.2
expert			0.3	0.2

Table 2 (*continued*)

Brain volumes (ml)	Mean	sd	Mean	sd
Intracranium	1454.4	123.8		
Total brain	1291.9	115.8		
Gray matter of the cerebrum	670.4	60.1		
White matter of the cerebrum	463.7	60.1		
Lateral ventricles	14.0	7.5		
Third ventricle	0.8	0.3		
Cerebellum	145.4	13.3		

[a] Total number of patients is 109. For some patients, not all interviews were completed.
[b] At inclusion, 15 patients were medication naive and no information was available for 28 patients.
[c] Between inclusion and follow-up, 2 patients did not use medication, although they did use medication before inclusion. No information was available for 30 patients.

The CAN assesses on 22 items whether there is a need for care according to a medical expert. The presence of a problem or a need is rated on a three-point scale. The total score of the CAN consists of the sum scores of all relevant needs divided by the number of needs. The mean scores of the different interviews are summarized in Table 2.

All interviewers from the three sites were trained before inclusion of patients started. There were regular contacts to ensure standard use of the interviews. From 79 patients, all measurements were completed at follow-up, while for 30 patients, one of the variables was not available.

2.4. Brain imaging

Magnetic resonance images were acquired on a 1.5 Tesla Philips NT scanner Release 5 (Best) in Utrecht and on 1.5 Tesla Siemens Magnetom Vision Scanners in Amsterdam (VB31C/D; Erlangen) and Groningen (VB31D; Erlangen). In Utrecht, a Three-Dimensional-Fast Field Echo (3D-FFE: TE = 4.6 ms, TR = 30 ms, flip angle = 30°, FOV = 256 × 256 mm^2) with 160–180 contiguous coronal 1.2 mm slices and a T2-weighted Dual Echo-Turbo Spin Echo (DE-TSE: TE1 = 14 ms, TE2 = 80 ms, TR = 6350 ms, flip angle = 90°, FOV = 256 × 256 mm^2) with 120 contiguous coronal 1.6 mm slices of the whole head were used for the quantitative measurements. In Groningen and Amsterdam, a Three-Dimensional-Fast Field Echo (3D-FFE: TE = 5 ms, TR = 30 ms, flip angle = 30°, FOV = 167 × 256 mm^2) with 160–180 contiguous coronal 1.2 mm slices of the whole head was acquired. In Groningen and Amsterdam, respectively, a T2-weighted Dual Echo-Turbo Spin Echo (DE-TSE: TE1 = 17 ms, TE2 = 102 ms, TR = 6510 ms, flip angle = 90°, FOV = 256 × 256 mm^2) with 100 contiguous coronal 2.0 mm slices of the whole head and a T2-weighted Dual Echo-Turbo Gradient Spin Echo (DE-TGSE: TE1 = 24 ms, TE2 = 99 ms,

Table 3
Mean (sd) volumetric measurements (cm^3), volume ratio, ICC, and correlation coefficient for each of the two sites with the reference site

	Intracranium	Total brain	Lateral ventricles	Third ventricle	Cerebellum	Gray matter cerebrum	White matter cerebrum
Utrecht	1425.33 (111.85)	1275.27 (83.77)	8.99 (2.55)	0.54 (0.16)	134.44 (8.09)	674.55 (51.55) calibrated:	453.81 (31.14) calibrated:
Groningen	1414.56 (89.04)	1296.52 (77.05)	9.29 (2.47)	0.52 (0.11)	138.03 (8.68)	684.30 (40.02)	462.08 (31.83)
	99.2%	101.7%	103.3%	96.3%	102.7%	101.4%	101.8%
	ICC = 0.95	ICC = 0.92	ICC = 0.98	ICC = 0.79	ICC = 0.89	ICC = 0.87	ICC = 0.93
	r = 0.98	r = 0.95	r = 0.98	r = 0.81	r = 0.97	r = 0.90	r = 0.96
Amsterdam	1424.81 (106.63)	1273.99 (83.04)	9.37 (2.61)	0.50 (0.08)	136.66 (10.28)	670.16 (50.13)	454.67 (25.53)
	100.0%	99.9%	104.2%	92.6%	101.7%	99.3%	100.2%
	ICC = 1.00	ICC = 0.99	ICC = 0.98	ICC = 0.67	ICC = 0.87	ICC = 0.95	ICC = 0.89
	r = 1.00	r = 0.99	r = 0.99	r = 0.82	r = 0.90	r = 0.94	r = 0.88

TR = 6400 ms, flip angle = 90°, FOV = 256 × 256 mm^2) with 100 contiguous coronal 2.0 mm slices of the whole head were acquired.

Post-processing was done on the neuro-imaging computer network of the Department of Psychiatry at the University Medical Center Utrecht, which includes Hewlett Packard Unix 9000 workstations, a compute server, and Pentium III personal computers. All images were coded to ensure blindness for subject identification. Scans were put into Talairach frame (no scaling), and corrected for inhomogeneities in the magnetic field (Sled et al., 1998). Volume measures of the intracranium, total brain, gray and white matter, cerebellum, third and lateral ventricles were determined. Quantitative assessment of the intracranial volume was performed with use of a full-automated computer program based on histogram analyses followed by mathematical morphological operators in the DE-TSE image. Quantitative assessment of the total brain, gray and white matter cerebrum volumes, cerebellar volume, and lateral and third ventricular volumes were performed based on histogram analyses followed by mathematical morphological operators in the 3D-FFE image, using the intracranial volume as mask (Schnack et al., 2001a,b). In addition, for the cerebellum and lateral and third ventricular volumes, anatomical knowledge-based selection principles were used. For the cerebellum, this included a plane perpendicular to the sagittal plane through the acquaduct. For the third ventricle, this included the coronal slices through the anterior commissure as anterior border, the coronal slice through the posterior commissure as posterior border, and a manually outlined roof to prevent leaks into the transverse cistern, drawn in the midsagittal reconstructed slice from a point superior to the thalamus and just inferior to the plexus choroideus. For the lateral ventricles, this included automated computer-incorporated anatomical knowledge of the anatomical location of the lateral ventricles in the brain (e.g., they are surrounded by white matter). All segmentations were checked after measurements and corrected manually if necessary. The interrater reliabilities of the volume measurements, determined by the Intraclass Correlation Coefficient (ICC) were 0.95 and higher.

The volumes of intracranium, total brain, gray and white matter of the cerebrum, third and lateral ventricles, and cerebellum are listed in Table 2.

2.5. Calibration of multi-center MRI scans

In MRI multi-center studies, variability of scanners and acquisition protocols between sites must be taken into consideration when measuring brain volumes. It was proposed that in MRI multi-center studies, the validity could be measured in a phantom while reliability should be measured in repeated measurements in human subjects and a phantom (Tofts, 1998). A validation and reliability study was performed since

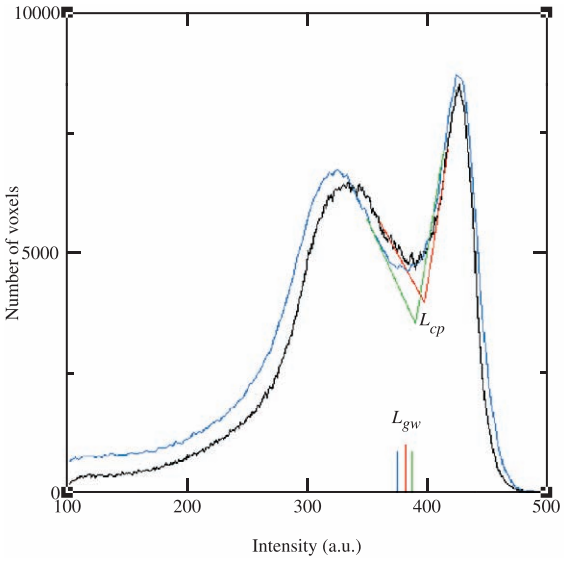

Fig. 1. Two typical intensity histograms of T1-weighted images are shown, calculated over the intracranial region (Utrecht in black; Amsterdam in blue). Third-degree polynomials were fitted to the histograms in the gray matter peak intensity range. For the white matter peaks, fifth-degree polynomials were fitted. Tangential lines to the steepest slope points were drawn (shown in red for Utrecht and shown in green for Amsterdam). The crossings of these lines mark the characteristic points L_{cp} of these histograms from which the gray/white thresholds are calculated by multiplying the characteristic point by a scaling factor. For images acquired by the scanner in Utrecht, this scaling factor f_{gw} was determined based on human raters manually setting gray/white thresholds. The gray/white threshold L_{gw} (red bar at the bottom; Schnack et al., 2001a) is the multiplication of this scaling factor (0.960) with L_{cp}. The gray and white matter volumes from the MR images made in Utrecht were taken as a reference. ICCs between the research sites and the reference site were calculated. For the images acquired by the scanners in Groningen and Amsterdam, the scaling factor f_{gw} was adjusted leading to the highest ICC between the sites (respectively $f_{gw} = 0.985$ and $f_{gw} = 0.995$). In the figure, a cyan bar shows the resulting threshold for Amsterdam with the Utrecht value of f_{gw} ($f_{gw} = 0.960$); with a green bar the optimal ($f_{gw} = 0.995$) threshold is shown.

scans of patients with recent-onset psychosis were conducted at three sites with 1.5 T MR scanners from two different manufactures (van Haren et al., 2001).

Five healthy volunteers (2 males/3 females, age range 20–35 years) and the Hoffman Brain Phantom (Hoffman et al., 1991) were scanned at the three sites. On all MR images, volumes of intracranium, total brain, third and lateral ventricles, cerebellum, and gray and white matter of the cerebrum were measured. The mean and standard deviation of the different brain volume measures were calculated for each site. Also, the means of the brain measures of the two sites were divided by the corresponding volumes of the reference site in order to calculate volume ratios. Reliability was measured by the Intraclass Correlation Coefficient (ICC). Table 3 shows the volume ratios and the ICCs. Furthermore, Pearson product moment correlation coefficients (r) were reported.

The "Utrecht method" of separating gray and white matter is dependent on a calibration factor, which is a constant for a fixed acquisition protocol, but which can differ for different protocols on different scanners. Therefore, the calibration factor was tuned to values for which the ICCs were maximal (ICC = 0.87 or higher). Separation of gray and white matter resulted in an overestimation of white matter and underestimation of gray matter of the brain scans of Amsterdam and Groningen. By applying a linear scaling procedure on the histogram (see Fig. 1), the volume ratios and ICCs improved considerably.

The phantom data revealed reasonably good face validity after comparison of the scaled intensity histograms (see Fig. 2).

In conclusion, repeated measurements in healthy control subjects and measuring a phantom are useful methods to determine comparability of brain volume measures in multicentre studies. All gray and white matter MRI data of the patient group were subsequently transformed to be comparable between sites.

2.6. Statistical analysis

Data were examined for outliers and extreme values and normality of the distribution. Duration of untreated psychosis was not normally distributed, so a square root transformation was performed. No further transformations were performed on the data.

To exclude the possibility that effects may have occurred because of differences between sites in the interactions between brain volume and outcome, an ANCOVA was carried out. Outcome measure (i.e., duration of hospitalization, the presence of negative

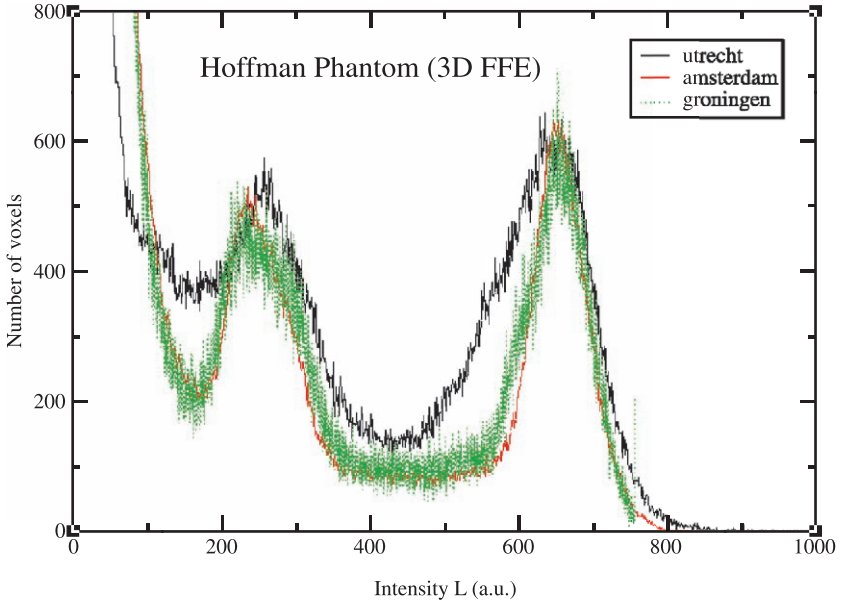

Fig. 2. Scaled intensity histograms of the Hoffman Brain phantom, showing relatively good face validity.

Table 4
No significant correlations ($p < 0.01$) were found between the MRI volume measurements and clinical variables at inclusion, corrected for intracranial volume, sex, and age

At inclusion	Duration of hospitalization before inclusion (months)	PANNS negative symptoms	GSDS social functioning
Cerebrum	− 0.09	0.08	0.10
Gray matter cerebrum	− 0.07	0.05	− 0.07
White matter cerebrum	− 0.05	0.06	0.22
Lateral ventricles	0.07	− 0.14	− 0.23
Third ventricle	0.12	0.03	0.05
Cerebellum	− 0.21	− 0.04	0.00

symptoms, social functioning, and need for care in daily functioning) was added as dependent variable, brain volume (i.e., volumes of total cerebrum, gray and white matter of the cerebrum, third and lateral ventricles, and cerebellum), intracranial volume, age and sex were added as covariates, and site was added as fixed factor.

Partial correlation analyses were calculated between MRI brain volume measurements and the baseline clinical variables that were later used as outcome measurement (i.e., negative symptoms, social functioning, and hospitalization before inclusion), corrected for intracranial volume, age, and sex. Partial correlation analyses of initial MRI brain volume measures (i.e., volumes of total cerebrum, gray and white matter of the cerebrum, third and lateral ventricles, and cerebellum) with outcome measures (i.e., duration of hospitalization, the presence of negative symptoms, social functioning, and need for care in daily functioning) were performed, corrected for intracranial volume, sex, and age. Correlation analyses between MRI and outcome measures were also controlled for cumulative medication between inclusion and follow-up, presence of drug abuse or dependence at inclusion, duration of untreated psychosis, and the relevant baseline measure. Correlations were not corrected for age of onset because age of onset was highly correlated with age at inclusion ($r = 0.97$, $p = 0.0001$).

3. Results

No significant differences were found between the sites in the interactions between brain volumes and outcome measures.

No significant partial correlations ($p <= 0.01$) were found between brain volume measurement and clinical variables at inclusion (see Table 4). Controlling for either duration of untreated psychosis, cumulative medication use before inclusion, or the presence of drug abuse or dependence at inclusion did not alter the results. As shown in Table 5, no significant partial correlations ($p <= 0.01$) were found between the outcome measures and MRI brain volumes measured at inclusion, after correction for age at inclusion, sex, and intracranial volume. Correction for total cumulative medication between inclusion and follow-up, the presence of drug dependence or drug abuse at inclusion, and duration of untreated psychosis did not change the results. For social functioning, negative symptoms, and duration of hospitalization, baseline measurements

Table 5
No significant correlations ($p < 0.01$) were found between the MRI volume measurements at inclusion and outcome, corrected for intracranial volume, sex, and age

At inclusion	At follow-up				
	CAN patient	expert	Duration of hospitalization since inclusion (months)	PANNS negative symptoms	GSDS social functioning
Cerebrum	0.09	0.07	0.05	− 0.06	0.07
Gray matter cerebrum	− 0.02	0.10	0.08	− 0.03	0.00
White matter cerebrum	0.15	− 0.01	− 0.01	− 0.05	0.09
Lateral ventricles	− 0.14	− 0.19	− 0.14	− 0.01	− 0.19
Third ventricle	0.03	0.03	0.09	0.07	0.00
Cerebellum	− 0.06	− 0.05	0.01	− 0.08	− 0.04

were available. Correcting for these baseline measurements did not change the results either.

4. Discussion

In this study, 109 schizophrenia patients in their first or second psychosis were included and followed for a mean of 1.8 years to investigate whether gray matter volume would predict outcome defined as duration of hospitalization, negative symptoms, social functioning, and need for care. In this large cohort, no correlations were found between gray matter volume of the cerebrum and outcome measures at follow-up. Although gray matter volume was reported to be decreased in chronically ill patients with poor outcome (Staal et al., 2001), no evidence was found for an association between decreased gray matter volume at illness onset and outcome after approximately 2 years of follow-up, suggesting there may be no relationship between gray matter volume and outcome in the early stages of the disease.

Moreover, no association was found between outcome and other brain volume measures, i.e., volumes of the cerebrum, white matter of the cerebrum, cerebellum, and third and lateral ventricles.

The analyses were controlled for several different possible confounding variables, i.e., presence of drug abuse or dependence, cumulative neuroleptic medication, duration of untreated psychosis, and the relevant baseline measurement. The effects of drug abuse or dependence on brain volumes in patients with schizophrenia are not clear. Each drug might have different effects on the brain. For example, there is evidence for brain shrinkage in alcoholics (Csernansky, 2001), while no effect on brain tissue volume was found in frequent marijuana users (Block et al., 2000). However, it is not known how these agents affect the brains of patients with schizophrenia. Also, the effects of neuroleptic medication on the interaction between brain volume measurements and outcome measurements are inconclusive. Gur et al. (1998) found that the changes in brain volume in first episode patients remained significant predictors of clinical improvement when medication dose was partialled out. Also, Cahn et al. (2002) found that loss of global gray matter was related to the disease process and, independent of that, to higher cumulative dosage of neuroleptic medication. Thus, it is unlikely that cumulative medication is masking the relationship between initial brain volume and outcome. Thirdly, duration of untreated psychosis has been found to predict outcome, even in the early stages of the illness (Malla et al., 2002). Finally, it might be that the patients with a second episode at baseline represent the poorer end of the outcome spectrum. Therefore, the relevant baseline measurement was included in the analysis. None of these possible confounds changed the relationship between brain volume measurements at inclusion and outcome measurements significantly after 2 years.

Our findings are in contrast to the finding of DeLisi et al. (1992) who reported a positive association between volume of lateral ventricles at illness onset and number of hospitalizations, duration of hospitalization and scores on the Brief Psychiatric Rating Scale in 30 recent-onset patients after a 2-year follow-up period. However, in a larger cohort ($n = 50$) and after a longer follow-up period (4–5 years), these associations were no longer evident (DeLisi et al., 1998). Thus, so far, no conclusive evidence is found for brain volume measurements at illness onset predicting outcome in the early stage of the disease.

Not finding an association between brain volume measures at illness onset and outcome may be a consequence of the relatively short follow-up period. Indeed, studies did find brain volume measures to predict outcome after 7 and 4 years, respectively (Wassink et al., 1999; Van Os et al., 1995). Although it has been suggested that the first 5 years after the first psychosis are characterized by the largest decline in functioning, followed by a relatively stable clinical period (Davidson and McGlashan, 1997), this also indicates that the disease is still very active during this time period and outcome may be particularly unstable. The variability in functioning during the early stage of the disease is also demonstrated by the clustering of most rehospitalizations within the first 2 years after first admission (Eaton et al., 1992a,b). Therefore, outcome might be fluctuating markedly in the early stages of the disease and reach a plateau only later. Because of this, some of the outcome measures used (i.e., negative symptoms, social functioning, and need for care) are influenced by a large amount of week-by-week (if not day-by-day) variation. In addition of normal measurement variation, this makes them not sensitive enough to pick up associations with brain

volumes. It may be that a relationship between outcome and brain volume measures will be found only when outcome is measured once a stable plateau has been reached.

Finally, it may be that a single MRI measurement might not be informative enough to find a relationship between brain volume measures at illness onset and outcome. In first episode patients, a few longitudinal MRI studies have been conducted examining multiple brain structures and their change over time (DeLisi et al., 1995, 1997; Gur et al., 1998; Lieberman et al., 2001; Wood et al., 2001; Puri et al., 2001; James et al., 2002). However, only one study used this information on changes in brain volume to predict outcome some time after the MRI follow-up. A decrease of cerebrum gray matter was found in 34 first episode patients compared to 36 healthy control subjects after a 1-year follow-up (Cahn et al., 2002). This decrement in gray matter was significantly correlated with outcome, measured 2 years after the first scan. Thus, one may speculate that changes in brain volumes over time, rather than brain volumes at a single point in time, may be more suited to predict outcome (in recent-onset) schizophrenia.

A limitation in this study is that only global gray matter measurements were acquired. In a meta-analysis of volumetric studies (Wright et al., 2000) and in a recent voxel-based morphometric study of gray matter density (Hulshoff Pol et al., 2001), it was found that gray matter is decreased in distinct focal areas in the brains of patients with schizophrenia, such as the amygdala and hippocampus, and several cortical areas. It might be that the volume of one of these structures would be found to predict outcome after approximately 2 years of follow-up in recent-onset schizophrenia.

In conclusion, our findings suggest that volume measurements of total cerebrum, gray and white matter of the cerebrum, third and lateral ventricles, and cerebellum do not predict outcome after 2 years of follow-up in recent-onset schizophrenia.

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