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ORIGINAL PAPER

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Cerebral atrophy and white matter disruption in chronic schizophrenia

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Abstract Several magnetic resonance imaging (MRI) studies have shown cerebral atrophy in established schizophrenia, although not in all reports. Discrepancies may mostly be due to population and post-processing differences. Recently, disruption of cortical white matter integrity has also been reported in chronic patients with schizophrenia. In this study we explored tridimensional (3D) cerebral volumes and white matter microstructure in schizophrenia with structural and diffusion magnetic resonance. Twenty-five patients with established schizophrenia and 25 1:1 matched normal controls underwent a session of MRI using a Siemens 1.5T-scanner. 3D brain volume reconstruction was performed with the semi-automatic software Amira (TGS, San Diego, CA), whereas the apparent diffusion coefficients (ADCs) of cortical white matter water molecules were obtained with in-house developed softwares written in MatLab (The Mathworks-Inc., Natick, MA). Compared to controls, patients with schizophrenia had significantly smaller gray matter intracranium and total brain volumes, increased 4th ventricle volumes, and greater temporal and occipital ADCs. Patients treated with typical antipsychotic medication ($N = 9$) had significantly larger right lateral and 4th ventricles compared to those on atypical antipsychotic drugs. Intracranial volumes significantly inversely correlated with left temporal ADC in patients with schizophrenia. Also, age correlated directly with right, left, and 3rd ventricle volumes and inversely with gray matter intracranium volumes in individuals with schizophrenia. This study confirmed the presence of cortical atrophy in patients with schizophrenia, especially in those on typical antipsychotic drugs, and the existence of white matter disruption. It also suggested that physiological aging effects on brain anatomy may be abnormally pronounced in schizophrenia.

Key words magnetic resonance · diffusion imaging · neuroimaging · brain imaging · ventricles · cerebellum · lobes

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Introduction

Magnetic resonance imaging (MRI) represents a non-invasive tool for in vivo studies of brain morphology, biochemistry and function in humans and has become the method of choice for investigation of brain,

because of its high contrast sensitivity and spatial resolution, in the absence of radiation exposure [13]. In the last 15 years, several MRI studies examined the brain anatomy in patients with schizophrenia in order to identify structural abnormalities [15, 30, 32, 50]. Particularly, cerebral atrophy and ventricular enlargement have been reported in chronic schizophrenia [25, 44, 69, 74], possibly being a sign of neurodegeneration [3, 38]. However, this has not been shown in all reports [59]. Conflicting findings may mainly be related to the lack of comparability between patients and controls for socio-demographical features and/or to different or inappropriate post-processing techniques amongst studies [74].

Recently, some diffusion weighted imaging (DWI) studies found white matter disruptions in chronic schizophrenia using the diffusion tensor imaging (DTI) technique [1, 5, 46, 51], potentially altering intra-hemispheric connectivity and functional brain lateralization [14, 17, 21, 22, 24, 27]. DWI is a relatively new technique capable of examining molecular water mobility in brain tissue by providing the apparent diffusion coefficient (ADC) of water molecules [66]. This is the critical measure for a detailed investigation of brain tissue integrity, particularly for white matter, providing information about microstructure, organization, and cytoarchitecture. DTI is obtained through the use of at least six non-collinear diffusion-weighed gradients, allowing the quantification of water molecule directionality other than water molecule mobility [9]. In neurologic disorders involving white matter, such as multiple sclerosis or stroke, ADC has been shown to be increased [12, 54, 57].

In this study we investigated with a tridimensional (3D) reconstruction technique total brain and ventricular size in patients with established schizophrenia compared to 1:1 matched normal individuals, expecting abnormally reduced volumes. Also, white matter microstructure was investigated with DWI along with an exploratory analyses of the relationship between white matter integrity and 3D volumes.

Methods

Subjects

Twenty-five DSM-IV patients with established schizophrenia (mean age ± SD = 40.60 ± 9.89 years; 14 males, 11 females; all right-handed Caucasians) (Table 1) identified from the South-Verona Psychiatric Care Register (PCR) [2, 65] were studied. Diagnoses for schizophrenia were obtained using the Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry (IGC-SCAN) [72] and confirmed with the clinical consensus of two staff psychiatrists. The IGC is a semi-structured standardized checklist of the SCAN encompassing 41 psychopathological item groups [70, 72], each of them including several symptoms. It was completed by two trained research clinical psychologists with extensive experience in doing SCAN. Indeed, they completed at least 10 IGC-SCAN with a well-trained senior investigator. Successively, they had to be fully reliable blindly and independently with the senior investigator, achieving similar diagnoses provided by the CATEGO software for at least 8 out of 10 IGC-SCAN. Moreover, the psychopathological item groups completed by the two raters were compared in order to discuss any major symptom discrepancies. Also, we regularly assured reliability of the IGC-SCAN diagnoses by holding consensus meeting with treating psychiatrists. It is worth noting that the Italian version of the SCAN was edited by our group [73] and that our investigators attended specific training courses held by official trainer in order to learn how to administer the IGC-SCAN. Also, our Center is a WHO Collaborating Center for Research and Training in Mental Health and Service Evaluation and is the only Italian WHO SCAN Training and Reference Center. Patients with comorbid psychiatric disorders, alcohol or substance abuse within the 6 months preceding the study, history of traumatic head injury with loss of consciousness, epilepsy or other neurological diseases were excluded. All patients were receiving antipsychotic medications at the time of imaging, of whom nine were on typical and 16 on atypical antipsychotic drugs. Specifically, 6 patients were on olanzapine (mean dose ± SD = 20.00 ± 3.76 mg/day), 6 on clozapine (mean dose ± SD = 445.83 ± 136.40 mg/day), 4 on risperidone (mean dose ± SD = 3.75 ± 2.36 mg/day), 4 on haloperidol (mean dose ± SD = 7.50 ± 8.34 mg/day), 2 on zuclopenthixol (75 mg/day and 100 mg/day, respectively), and the remaining 3 on other typical antipsychotics (fluphenazine, clotiapine, and chlorpromazine). Patients' clinical information was retrieved from psychiatric interviews, the attending psychiatrist, and medical charts and clinical symptoms were characterized using the Brief Psychiatric Rating Scale (BPRS 24-item version) [67]. The BPRS was administered by two trained research clinical psychologists and the reliability was established and monitored utilizing similar procedures as to the IGC-SCAN.

Table 1 Socio-demographical and clinical variables for normal controls and patients with schizophrenia

	Normal controls (N = 25)	Schizophrenia patients (N = 25)	Statistics	P
Age (years)	40.20 ± 10.71	40.60 ± 9.89	t = −0.14	0.89
Males/Females	14/11	14/11		
Right-handed	25	25		
Race	Caucasian	Caucasian		
Weight (kg)	70.20 ± 10.42	76.48 ± 19.33	t = −1.43	0.16
Height (cm)	171.52 ± 8.93	169.60 ± 7.99	t = 0.80	0.43
Primary or secondary school/high school/bachelor or professional school	14/6/5	18/7/0	χ^2 = 5.58	0.06
Age at onset (years)	–	25.61 ± 7.23		
Length of illness (years)	–	15.20 ± 8.29		
Number of hospitalizations	–	5.68 ± 9.00		
Lifetime AP treatment (years)	–	12.32 ± 7.81		
BPRS total score	–	50.59 ± 17.98		

AP, antipsychotic; BPRS, Brief Psychiatric Rating Scale

Twenty-five normal controls 1:1 matched with patients for race, age, gender, and handedness were also recruited (mean age ± SD = 40.20 ± 10.71 years; 14 male, 11 females; all right-handed Caucasians). Control individuals had no DSM-IV axis I disorders, as determined by an interview modified from the SCID-IV non-patient version (SCID-NP), no history of psychiatric disorders among first-degree relatives, no history of alcohol or substance abuse and no current major medical illness. Normal controls were people working in the hospital or in the University in any kind of staff, such as office boys, administrative assistants, secretaries, nurses, or physicians. They participated in the study as volunteers and had no evidence of central nervous system abnormalities on the scan, as reviewed by the neuroradiologist (R.C.).

This research study was approved by the biomedical Ethics Committee of the Azienda Ospedaliera of Verona. All individuals provided signed informed consent, after having understood all issues involved in study participation.

MRI procedure

MRI scans were acquired with a 1.5T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B. A standard head coil was used for RF transmission and reception of the MR signal and restraining foam pads were utilized for minimizing head motion. T1-weighted images were first obtained to verify subject's head position and image quality (TR = 450 ms, TE = 14 ms, flip angle = 90°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 384 × 512). PD/T2-weighted images were then acquired (TR = 2,500 ms, TE = 24/121 ms, flip angle = 180°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 410 × 512), according to an axial plane parallel to the anterior–posterior commissures (AC-PC), for clinical neurodiagnostic evaluations (exclusion of focal lesions). Subsequently, a coronal 3D MPR sequence covering the entire brain was acquired (TR = 2,060 ms, TE = 3.9 ms, flip angle = 15°, FOV = 176 × 235, slice thickness = 1.25 mm, matrix size = 270 × 512). Diffusion weighted echoplanar images were acquired using same parameters for $b = 0$, $b = 1{,}000$, and ADC maps in the axial plane parallel to the AC-PC line (TR = 3,200 ms, TE = 94 ms, FOV = 230 × 230, slice thickness = 5 mm with 1.5 mm gap, matrix size = 128 × 128) and in the coronal plane from the frontal to the occipital lobes (TR = 5,000 ms, TE = 94 ms, FOV = 230 × 230, slice thickness = 4 mm with 0.4 mm gap, matrix size = 128 × 128). Specifically, three-gradient were acquired in three orthogonal directions.

Image analyses

Images were displayed on a commercial PC workstation for the post-processing analyses. Tridimensional (3D) volumes were traced manually in the coronal, sagittal, and axial plane using the semi-automated software Amira software (Amira Software 3.1, TGS Inc., San Diego, CA, USA) in reference to standard brain atlases [34, 55] (Figs. 1, 2). For gray/white matter segmentation, the coronal slice where optic chiasma was clearly visible was chosen. Then, the same lowest voxel value detected in both corpus callosum and internal capsule was utilized to separate gray from white matter, which were successively automatically obtained by Amira.

The apparent diffusion coefficients (ADC) of water molecules were detected by using in-house developed softwares written in MatLab (version 7; The Mathworks Inc., Natick, MA). ADCs were obtained by placing, bilaterally, circular regions of interest (ROI) in the frontal, temporal, parietal, and occipital lobes on the non-diffusion weighted ($b = 0$) echoplanar images according to Wolkin et al. [71] (Fig. 3). Then, they were automatically transferred to the corresponding maps to obtain the ADCs, which were obtained from the diffusion images with $b = 1{,}000$ according to the following equation: $-b\mathrm{ADC} = \ln [A(b)/A(0)]$. Specifically, $A(b)$ is the measured echo magnitude, b is the measure of diffusion weighting and $A(0)$ is the echo magnitude without diffusion gradient applied [9]. The resulting ADC was expressed in units of 10^{-5} mm^2/s.

A trained rater (N.A.) blind to group assignment and patients' identities measured all scans. The intra-class correlation coefficients (ICCs) were calculated for both 3D volumes and white matter

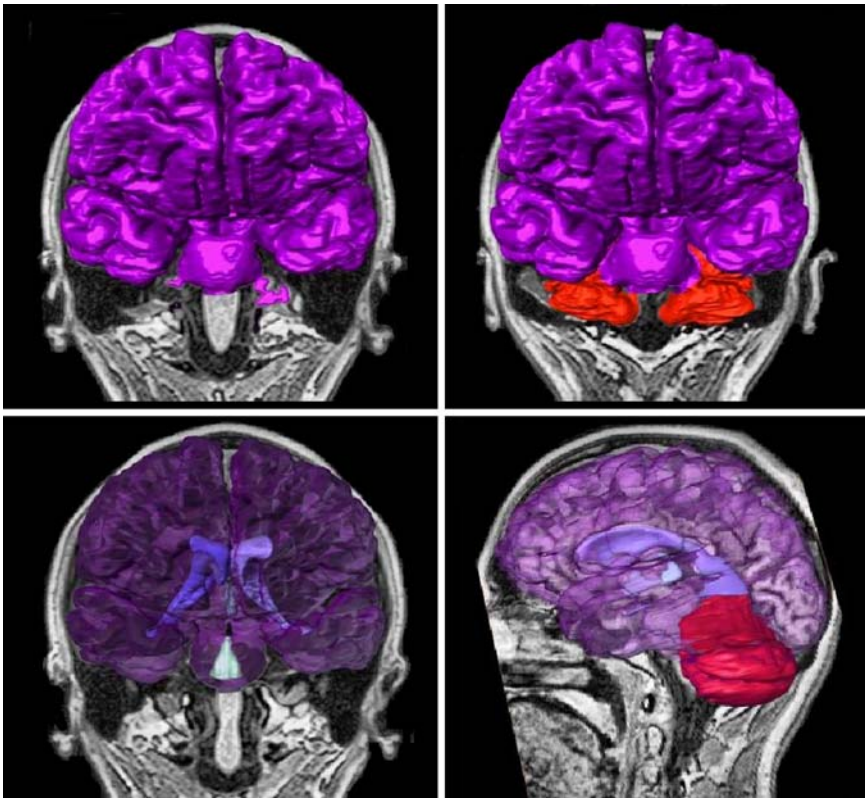

Fig. 1 Tridimensional (3D) volume reconstruction for brain, cerebellum, and ventricles. Tridimensional volumes are reported in violet for brain, in red for cerebellum and in blue for ventricles

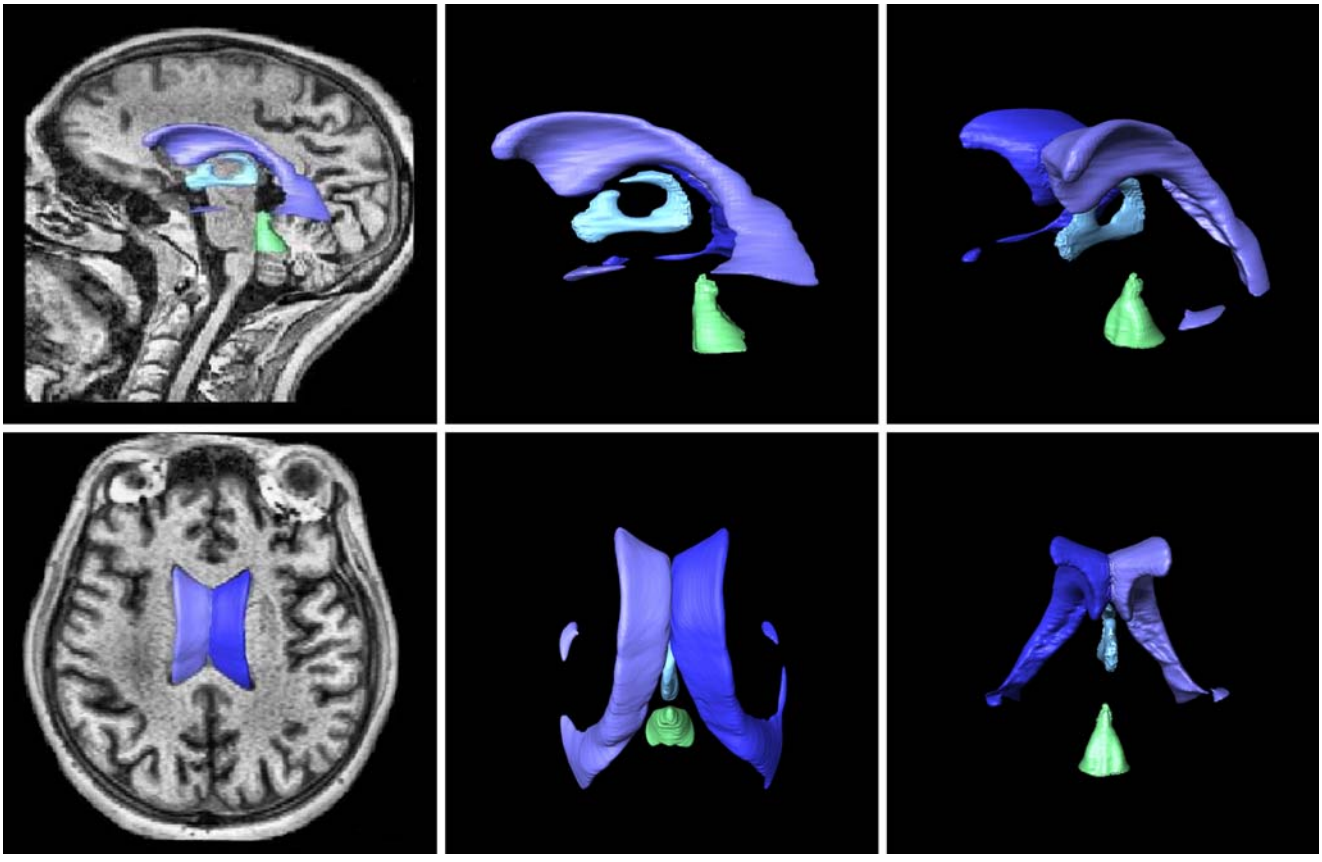

Fig. 2 Tridimensional (3D) volume reconstruction for ventricle system. Lateral, 3rd and 4th ventricle are shown separately (blue: right lateral ventricle; violet: left lateral ventricle; light blue: 3rd ventricle; green: 4th ventricle)

ADCs by having two independent raters trace 10 training scans (N.A and G.M., N.A. and A.V., respectively). Specifically, the ICCs were $r = 0.94$ for intra-cranial volumes, $r = 0.091$ for total brain volumes, $r = 0.99$ for right and left lateral ventricle volumes, $r = 0.90$ for 3rd and 4th ventricle volumes, $r = 0.96$ for cerebellum, $r = 0.72$ for gray/white matter separation, $r = 0.97$ and $r = 0.93$ for right and left frontal ADCs, $r = 0.91$ and $r = 0.97$ for right and left temporal ADCs, $r = 0.92$ and $r = 0.93$ for right and left parietal ADCs, and $r = 0.91$ and $r = 0.90$ for right and left occipital ADCs, respectively.

Anatomical landmarks

3D volumes

Intra-cranial volumes: tracing started from the first slice that contained brain matter until the last one, considering all slices; we traced around the brain, including everything other than optic chiasma, ventricle system, and subarachnoid space. Total brain volumes and cerebellum: a line connecting the cerebellar peduncles separated total brain from cerebellum. Ventricle system: the interventricular foramen delimitated the lateral ventricles and the 3rd ventricle; whereas the 3rd and the 4th ventricle were separated by the aqueduct of Sylvius, which was included in the 4th ventricle.

White matter ROIs

Frontal lobe: ROIs were placed in the axial slice at the level of the genu of corpus callosum (standardized at 43.5 mm^2), then in the inferior one (standardized at 43.5 mm^2) and in the two superior slices (standardized at 84.4 mm^2), posteriorly and medially to the frontal horns of the lateral ventricles. Parietal lobe: ROIs (standardized at 84.4 mm^2) were placed in the axial slice when the lateral ventricles first disappeared and were positioned posteriorly to the postcentral sulcus. Temporal lobe: ROIs (standardized at 43.5 mm^2) were placed in the axial slice at the level of the lateral fissure and in the inferior slice, posteriorly and laterally to the lateral fissure. Occipital lobe: ROIs (standardized at 43.5 mm^2) were placed in the two inferior axial slices where the occipital horns of the lateral ventricles become visible, posteriorly to the occipital horns.

Statistical analyses

All analyses were conducted using the SPSS for Windows software, version 11.0 (SPSS Inc., Chicago), and the 2-tailed statistical significance level was set at $P < 0.05$. The Student t-test was used to compare intracranium, total brain, cerebellum, and white matter ADCs between schizophrenia patients and normal control, whereas ANCOVA with intracranium volume as covariate was performed for ventricle measures. Pearson's correlation and partial correlation analyses controlled for age were used to examine possible association between age and clinical variables, respectively, and 3D or ADC measures. Also, partial correlation analyses controlled for age were performed to explore the relationship between total brain and ventricular volumes and ADC values. In this case, due to multiple comparisons, the 2-tailed statistical significance level was set at $P < 0.01$.

Results

Compared to normal controls, patients with schizophrenia had significantly lower total and gray matter

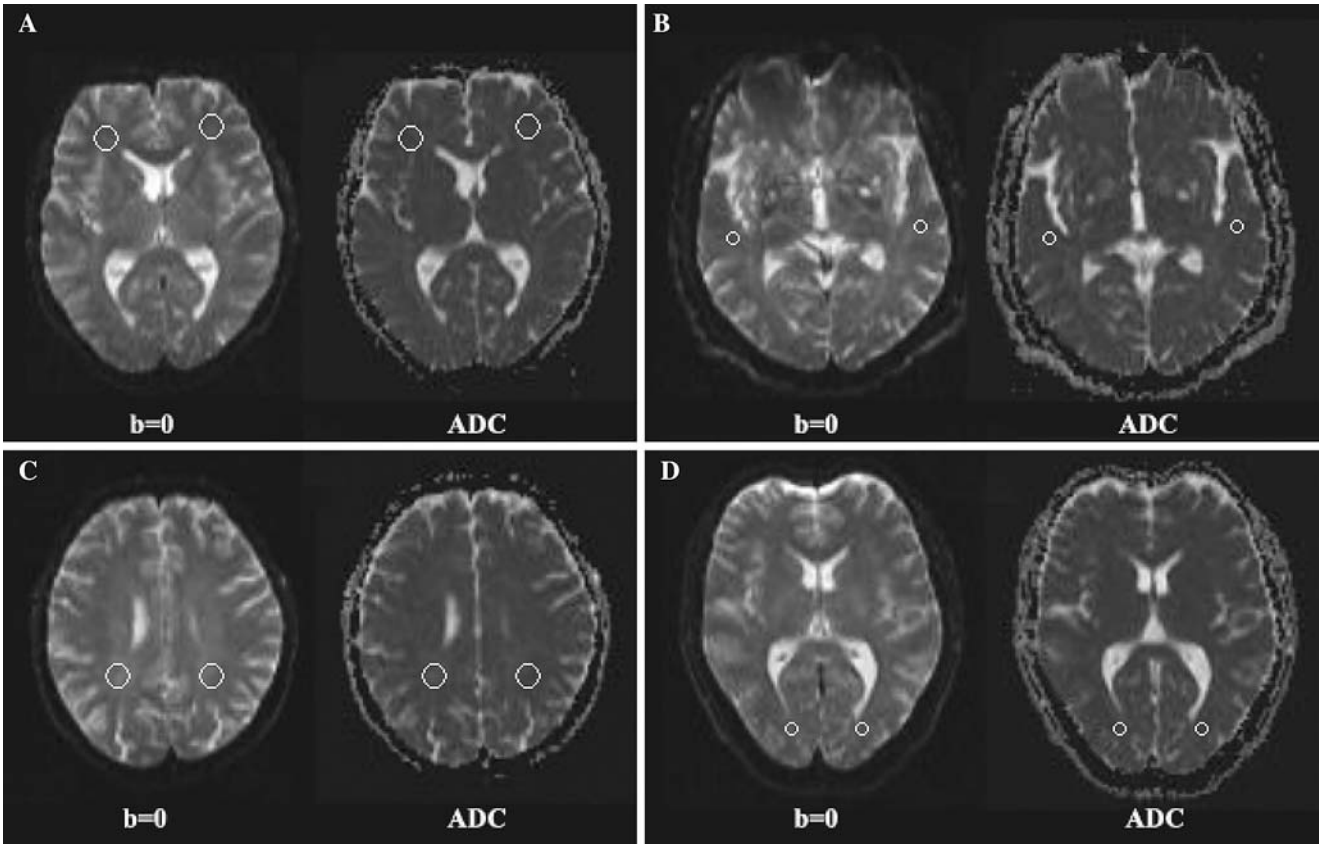

Fig. 3 Regions of interest placed in white matter. Circular regions of interest (ROI) were placed in white matter on the $b = 0$ echoplanar images, and then automatically transferred in ADC maps (A: frontal lobes; B: temporal lobes; C: parietal lobes; D: occipital lobes)

intra-cranial volumes ($t = 2.73$ $P < 0.01$ and $t = 2.36$, $P = 0.02$, respectively) and total brain volumes ($t = 2.74$, $P < 0.01$) and significantly increased 4th ventricle volumes ($F = 7.94$, $P < 0.01$). No statistically significant differences were found between the two groups for the remaining 3D volumes ($P > 0.05$; Table 2). Interestingly, patients treated with typical antipsychotic medication ($N = 9$) had significantly larger right lateral and 4th ventricle volumes and trend for significantly larger left lateral and 3rd ventricle size compared to patients on atypical antipsychotic drugs ($N = 16$) ($F = 7.27$, $P = 0.01$; $F = 5.17$, $P = 0.03$; $F = 3.79$, $P = 0.06$; $F = 3.74$, $P = 0.07$, respectively) (ANCOVA with intra-cranium volume as covariate).

Also, subjects suffering from schizophrenia had significantly greater apparent diffusion coefficients (ADCs) for temporal and occipital white matter compared to normal individuals, in both right and left side (temporal ADCs: $t = -2.44$, $P = 0.01$ and $t = -2.67$, $P = 0.01$; occipital ADCs: $t = -2.69$, $P < 0.01$ and $t = -3.3$, $P < 0.01$, respectively), but not for bilateral frontal and parietal ADCs (student t-test, $P > 0.05$) (Table 3). Left temporal ADCs were signif-

Table 2 Tridimensional (3D) volumes in normal controls and patients with schizophrenia

Volumes (ml)	Normal controls ($N = 25$)	Schizophrenia patients ($N = 25$)	Statistics	P
Total intra-cranium	1133.64 ± 93.87	1057.65 ± 102.44	$t = 2.73$	<0.01
Gray matter intra-cranium	631.56 ± 72.74	585.80 ± 64.40	$t = 2.36$	0.02
White matter intra-cranium	501.97 ± 101.77	471.85 ± 95.69	$t = 1.08$	0.29
Total brain	1007.06 ± 85.12	938.21 ± 92.56	$t = 2.74$	<0.01
Cerebellum	126.58 ± 13.76	119.44 ± 17.77	$t = 1.59$	0.12
Right lateral ventricle	7.96 ± 5.13	7.59 ± 3.53	$F = 0.02$	0.89
Left lateral ventricle	8.00 ± 5.16	8.34 ± 4.04	$F = 0.34$	0.56
3rd ventricle	1.22 ± 0.75	1.44 ± 0.59	$F = 1.83$	0.18
4th ventricle	1.09 ± 0.48	1.36 ± 0.41	$F = 7.94$	<0.01

Student t-test was used to compare intra-cranium, total brain, and cerebellum volumes between the two groups, whereas ANCOVA with intra-cranium volume as covariate was performed for ventricles

Table 3 Apparent diffusion coefficient (ADC) measures for white matter in normal controls and patients with schizophrenia

Apparent diffusion coefficients (ADC)	Normal controls ($N = 25$)	Schizophrenia patients ($N = 25$)	Statistics	P
Right frontal lobe	75.31 ± 3.70	76.79 ± 4.69	$t = -1.24$	0.22
Left frontal lobe	72.43 ± 3.65	74.05 ± 5.14	$t = -1.28$	0.21
Right temporal lobe	75.71 ± 5.35	79.75 ± 6.34	$t = -2.44$	0.01
Left temporal lobe	75.45 ± 5.62	80.19 ± 6.89	$t = -2.67$	0.01
Right parietal lobe	71.95 ± 5.26	71.21 ± 4.71	$t = 0.52$	0.60
Left parietal lobe	73.32 ± 4.69	73.35 ± 3.71	$t = -0.03$	0.98
Right occipital lobe	78.53 ± 5.29	83.34 ± 7.18	$t = -2.69$	<0.01
Left occipital lobe	76.03 ± 4.51	80.41 ± 4.87	$t = -3.30$	<0.01

Student t-test was used to analyze ADCs between the two groups, which was measured in 10^{-5} mm^2/s

icantly inversely correlated with intra-cranial volumes in patients with schizophrenia, but not in healthy controls (partial correlation coefficient = −0.53, $P = 0.008$; partial correlation coefficient = −0.41, $P = 0.044$, respectively). The remaining ADC values did not significantly associated with 3D total brain or ventricular volumes in schizophrenia or control group (Partial correlation coefficient controlled for age, $P > 0.01$).

Age correlated directly with right lateral, left lateral, and 3rd ventricle volumes and inversely with gray matter intra-cranial volumes in individuals with schizophrenia ($r = 0.66$, $P < 0.001$; $r = 0.55$, $P < 0.01$; $r = 0.46$, $P = 0.02$; $r = -0.49$, $P = 0.01$, respectively), but not in normal controls (Pearson's correlation, $P > 0.05$). These associations with age were still significant in subjects with schizophrenia, except for 3rd ventricle volumes, when the administration of typical or atypical antipsychotic drugs was taken into consideration (Partial correlation coefficient controlled for antipsychotic type, $P < 0.05$). No significant associations were shown between clinical variables (age at onset, length of illness, number of hospitalizations, BPRS scores, antipsychotic lifetime treatment) and 3D volumes or white matter ADCs (partial correlation controlled for age, $P > 0.05$).

Discussion

This study reported cerebral atrophy in established schizophrenia, consistently with previous original controlled MRI studies [19, 33, 47, 58] and systematic reviews/meta-analyses [44, 69, 74]. Interestingly, a significant inverse correlation between intra-cranium volumes and left temporal ADC was found in patients with schizophrenia, suggesting that white matter deficits in this area may specifically participate in reducing total brain volumes in schizophrenia. Moreover, patients treated with typical antipsychotic medications had larger ventricular system compared to those on atypical antipsychotic drugs. This is in line with recent data showing more severe impairment of brain morphology in patients on typical antipsychotic compared to those on atypical ones [45]. Moreover, an abnormal enlargement of 4th ventricle in patients with schizophrenia was shown which was also found by some [6, 36, 62], but not all previous MRI studies [35, 49]. The conflicting findings shown in the literature for cortical atrophy or 4th ventricle enlargement may be due to methodological differences amongst reports, mostly related to population socio-demographical features and/or to post-processing techniques [74]. We were able to overcome these limitations by recruiting very well matched groups and by using a 3D reconstruction method, which allows better fine anatomical delimitation than conventional bidimensional (2D) tracing technique.

Additionally, we found temporal and occipital white matter disruption in schizophrenia, as shown by higher ADCs. Consistently, abnormalities of temporo-occipital white matter integrity have been found in chronic schizophrenia by prior small diffusion imaging reports [40], as reflected by abnormally increased water diffusion coefficient [4] or abnormally decreased fractional anisotropy (FA) [1, 5, 46, 51]. FA was not obtained in this study, since the diffusion tensor sequence was not collected. Anyway, both ADC and FA are considered complementary non-specific index of white matter microstructure organization, providing evidences of disruption when increased and decreased, respectively [9, 66]. This may be due to reduced axonal density or myelination, being also oligodendrocytes, which have the potential to influence myelination and synaptic transmission, functionally abnormal in schizophrenia [20, 23]. Moreover, although several factors may contribute to explain increased water white matter diffusion, such as less dense packing of fibers, disruption of internal axonal integrity (reduced intra-axonal microtubular density), reduced degree of myelination, or variation of membrane permeability to water, the density of axonal membranes and myelin seem to play the major role [10].

In this study we did not find frontal white matter disruption in schizophrenia, which is a crucial area for the pathophysiology of the disease [39]. In contrast, this has consistently been shown by several [5, 16, 31, 41, 43, 51, 64, 68], although not all diffusion imaging studies [28, 61, 63]. It should be noted that the majority of our patients ($N = 16$ out of 25) were treated with atypical antipsychotic medications,

which have recently been found to preserve brain volumes and functions in schizophrenia, particularly those related to prefrontal regions [11, 45, 52]. Therefore, atypical antipsychotic drugs may potentially have protected from frontal white matter disruption. Nonetheless, the relatively modest sample size may have limited our ability to detect subtle abnormalities of frontal white matter miscrostructure. We would thus expect to find frontal white matter disruption in schizophrenia by increasing the size of our sample.

Additionally, age significantly correlated with gray matter intra-cranium volumes (inversely) and lateral ventricle volumes (directly) in patients with schizophrenia, independently of typical or atypical antipsychotic administration, but not in normal individuals. These findings may indicate a more pronounced age-related cerebral atrophy and ventricular enlargement in schizophrenia, which may be of relevance for the pathophysiology of the disorder. Therefore, the physiological effects of brain aging may be faster in patients with schizophrenia compared to normal controls [7, 8], as shown in previous studies [26, 29, 48, 53, 56, 60].

Some limitations should be taken into consideration. First of all, our patient sample was composed by treated patients with established schizophrenia, thus it is not completely clear whether the brain abnormalities preceded the onset of the illness, or appeared subsequently as a result of illness course or psychotropic treatment. However, no significant effects of length of illness or antipsychotic lifetime administration were found on 3D volumes or ADC values. Second, our approach did not detect particular fronto-temporal or fronto-parietal white matter fiber tracts [18, 37, 42]. Last, it cannot completely be excluded that, due to the proximity of the occipital ROI to the occipital horn of the lateral ventricles, partial volume effect may have altered occipital ADC values in subjects with schizophrenia. However, this should have happened for healthy controls as well, eventually removing this potential confounding factor. Furthermore, adjacent slices were checked to ensure that partial volume effects were minimized. Anyway, two particular strengths of our study should be noted, i.e., (1) the investigation of brain volumes and white matter integrity using a 3D reconstruction technique and diffusion imaging, respectively, and (2) the comparison of schizophrenia patients with control individuals 1:1 matched for age, gender, race, and handedness.

In conclusion, the presence of cortical atrophy in schizophrenia has been confirmed along with the suggestion that physiological aging effects on brain anatomy may be more pronounced in individuals with schizophrenia compared to normal controls. Moreover, this study found temporo-occipital disruption of white matter, which may potentially alter intra-hemispheric communication in patients suffering from schizophrenia. Future longitudinal MR studies should further explore these issues in larger population of chronic and first-episode patients with schizophrenia.

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