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Cortical white-matter microstructure in schizophrenia

Diffusion imaging study

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Background Several, although not all, of the previous small diffusion-weighted imaging (DWI) studies have shown cortical white-matter disruption in schizophrenia.

Aims To investigate cortical white-matter microstructure with DWI in a large community-based sample of people with schizophrenia.

Method Sixty-eight people with schizophrenia and 64 healthy controls underwent a session of DWI to obtain the apparent diffusion coefficient (ADC) of white-matter water molecules. Regions of interest were placed in cortical lobes.

Results Compared with controls, the schizophrenia group had significantly greater ADCs in frontal, temporal and occipital white matter (analysis of covariance, $P<0.05$).

Conclusions Our findings confirm the presence of cortical white-matter microstructure disruption in frontal and temporo-occipital lobes in the largest sample of people with schizophrenia thus for studied with this technique. Future brain imaging studies, together with genetic investigations, should further explore white-matter integrity and genes encoding myelin-related protein expression in people with first-episode schizophrenia and those at high risk of developing the disorder.

Declaration of interest None.

Diffusion-weighted imaging (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 (Taylor *et al*, 2004), particularly in white matter, a highly organised tissue where water diffusion is restricted. The ADC is the critical measure for a detailed investigation of white-matter integrity and inferences can be drawn from it on white-matter microstructure, organisation and cytoarchitecture, which cannot be visualised using conventional magnetic resonance imaging (Basser, 2002). When brain tissue is disrupted, such as in neurological disorders involving white matter (for example multiple sclerosis), the ADC is abnormally increased (Nusbaum *et al*, 2000; Rovaris *et al*, 2002). Recently DWI has been used to explore white matter in schizophrenia, since this tissue has been suggested to have a major role in the pathophysiology of this disorder (Keshavan, 1999; Keshavan *et al*, 2005). Indeed, white-matter changes may alter intra-hemispheric connectivity and functional brain lateralisation in people with schizophrenia (Falkai *et al*, 1995; DeLisi *et al*, 1997; Crow, 1998; Brambilla *et al*, 2005), potentially sustaining cognitive deficits. Several DWI studies conducted in recent years have consistently shown cortical white-matter disruptions (Taylor *et al*, 2004), although not all investigations have done so (Steel *et al*, 2001; Foong *et al*, 2002; see Table DS1 to the online version of this paper). However, previous diffusion imaging reports were limited by small sample sizes.

We used DWI to investigate cortical white-matter microstructure in a large community-based sample of patients with schizophrenia recruited from the geographically defined catchment area of South Verona in Italy. Our hypothesis, based on previously published findings of disrupted white-matter integrity in schizophrenia, was that people with schizophrenia would have increased ADC values.

METHOD

Sample

Sixty-eight people with a DSM–IV diagnosis of schizophrenia (American Psychiatric Association, 1994) were studied (Table 1). They were recruited from the geographically defined catchment area of South Verona (100 000 inhabitants) and treated by the South Verona community-based mental health service and by other clinics reporting to the South Verona Psychiatric Care Register (Amaddeo *et al*, 1997; Tansella & Burti, 2003). Diagnoses of schizophrenia were obtained using the Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry (IGC–SCAN; World Health Organization, 1992) and confirmed with the clinical consensus of two staff psychiatrists. The IGC–SCAN assessments were completed by two trained research clinical psychologists (C.P., L.P.) with extensive experience in using the SCAN instrument. They completed at least ten IGC–SCAN ratings with a senior investigator trained in SCAN assessment, after having conducted several IGC–SCAN assessments. Successively, reliability was checked in a further ten assessments with the senior investigator, masked to the results. Similar diagnoses were obtained for at least eight out of ten IGC–SCAN assessments. Moreover, the psychopathological item groups completed by the two raters were compared in order to discuss any major symptom discrepancies. In addition, we regularly assured reliability of the IGC–SCAN diagnoses by holding consensus meetings with treating psychiatrists and a senior investigator. It is noteworthy that the Italian version of the SCAN was edited by our group (World Health Organization, 1996) and that our investigators attended specific training courses held by an official trainer in order to learn how to administer the IGC–SCAN. Subsequently, diagnoses of schizophrenia were corroborated with the clinical consensus of two staff psychiatrists, according to DSM–IV criteria. Patients with a comorbid psychiatric disorder, alcohol or substance misuse within the 6 months preceding the study, a history of traumatic head injury with loss of consciousness, or epilepsy or other neurological diseases were excluded. All but two patients were receiving antipsychotic medication at the time of imaging. Specifically, 22 patients were taking typical antipsychotic drugs (13 haloperidol, 3 chlorpromazine, 2 fluphenazine,

Table 1 Socio-demographic and clinical variables of the sample

	Control group (n=64)	Schizophrenia group (n=68)
Age, years: mean (s.d.)	40.70 (11.16)	41.39 (11.68)
Males/females, *n*	34/30	39/29
Right-handed	60	64
Ethnicity, %		
White	100	100
Education, *n*		
Primary or secondary school	22	51***
High school	15	15
First degree or professional school	27	2
Clinical variables: mean (s.d.)		
Age at onset, years		27.46 (9.48)
Length of illness, years		14.40 (11.12)
Number of hospitalisations		3.79 (6.09)
Lifetime antipsychotic treatment, years		12.83 (10.76)
BPRS score		
Total		45.38 (16.96)
Negative symptom score		9.08 (3.13)
Positive symptom score		11.74 (6.68)

Brief Psychiatric Rating Scale.
***χ^2=33.31, P<0.001.

2 clotiapine, 1 thioridazine, 1 zuclopenthixol) and 44 on atypical antipsychotic medication (25 on olanzapine, 9 on clozapine, 8 on risperidone, 2 on quetiapine). Patients' clinical information was retrieved from psychiatric interviews, the attending psychiatrist and medical charts. Clinical symptoms were characterised using the 24-item Brief Psychiatric Rating Scale (BPRS; Ventura *et al*, 2000), which was administered by two trained research clinical psychologists (C.P., L.P.). The reliability of the BPRS ratings was established and monitored using similar procedures to those used for the IGC–SCAN.

Sixty-four people were recruited to constitute a healthy control group (Table 1). They had no DSM–IV Axis I disorder, as determined by an interview modified from the Structured Clinical Interview – DSM–IV Axis I Disorders, non-patient version (Spitzer & Williams, 1988), no history of psychiatric disorder in a first-degree relative, no history of alcohol or substance misuse and no current major medical illness. Members of the control group were hospital or university staff volunteers or patients undergoing magnetic resonance imaging (MRI) for dizziness without evidence of central nervous system abnormalities on the scan, as reviewed by the neuroradiologist (R.C.); their dizziness was due to benign paroxysmal positional vertigo or to non-toxic labyrinthitis. Control group participants were scanned only after a full medical history and general neurological, otoscopic and physical examinations, and after they had completely recovered from their dizziness. None was taking any medication at the time of participation, including drugs for nausea or vertigo.

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.

Imaging procedure

The MRI scans were acquired with a 1.5 T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B (http://www.medical.siemens.com). A standard head coil was used for radiofrequency transmission and reception of the MR signal and restraining foam pads were used to minimise head motion. First, T_1-weighted images were obtained to verify the participant's head position and the image quality: repetition time (TR) 450 ms, time to echo (TE) 14 ms, flip angle 90°, field of view (FOV) 230 mm × 230 mm, 18 slices, slice thickness=5 mm, matrix size 384 mm × 512 mm. Proton density T_2–weighted images were then acquired (TR= 2500 ms, TE=24/121 ms, flip angle 180°, FOV 230 mm × 230 mm, 20 slices, 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, diffusion-weighted echoplanar images were acquired in the axial plane parallel to the AC–PC line (TR=3200 ms, TE=94 ms, FOV 230 mm × 230 mm, 20 slices, slice thickness 5 mm with 1.5 mm gap, matrix size 128 mm × 128 mm; these parameters were the same for b=0, b=1000 and the ADC maps) and in the coronal plane from the frontal to the occipital lobes (TR=5000 ms, TE= 94 ms, FOV 230 mm × 230 mm, 30 slices, slice thickness 4 mm with 0.4 mm gap, matrix size 128 × 128; these parameters were the same for b=0, b=1000 and the ADC maps). Specifically, diffusion-weighted MRI was performed in three orthogonal directions during all sequences.

Image analyses

The apparent diffusion coefficients of water molecules for cortical white matter were detected by using software developed in-house written in MatLab version 7 (The Mathworks, Natick, Massachusetts, USA). The ADCs were obtained by placing, bilaterally, circular regions of interest in the frontal, temporal, parietal and occipital cortex on the non-diffusion-weighted (b=0) echoplanar images in reference to standard brain atlases (Jackson & Duncan, 1996; Patel & Friedman, 1997) and according to previous studies (Sun *et al*, 2003; Wolkin *et al*, 2003; Kumra *et al*, 2004; Kitamura *et al*, 2005; Fig. 1). The regions of interest were then automatically transferred to the corresponding maps to obtain the ADCs. The ADC maps were obtained from the diffusion images with b=1000, according to the equation $b_{ADC}=\ln[A(b)/A(0)]$, where $A(b)$ is the measured echo magnitude, b is the measure of diffusion weighting and $A(0)$ is the echo magnitude without diffusion gradient applied (Basser, 2002). The resulting ADC was expressed in units of 10^{-5} mm²/s. A trained rater (N.A.), masked to group assignment and patient identity, measured all scans. The intraclass correlation coefficients, which were calculated by having two independent

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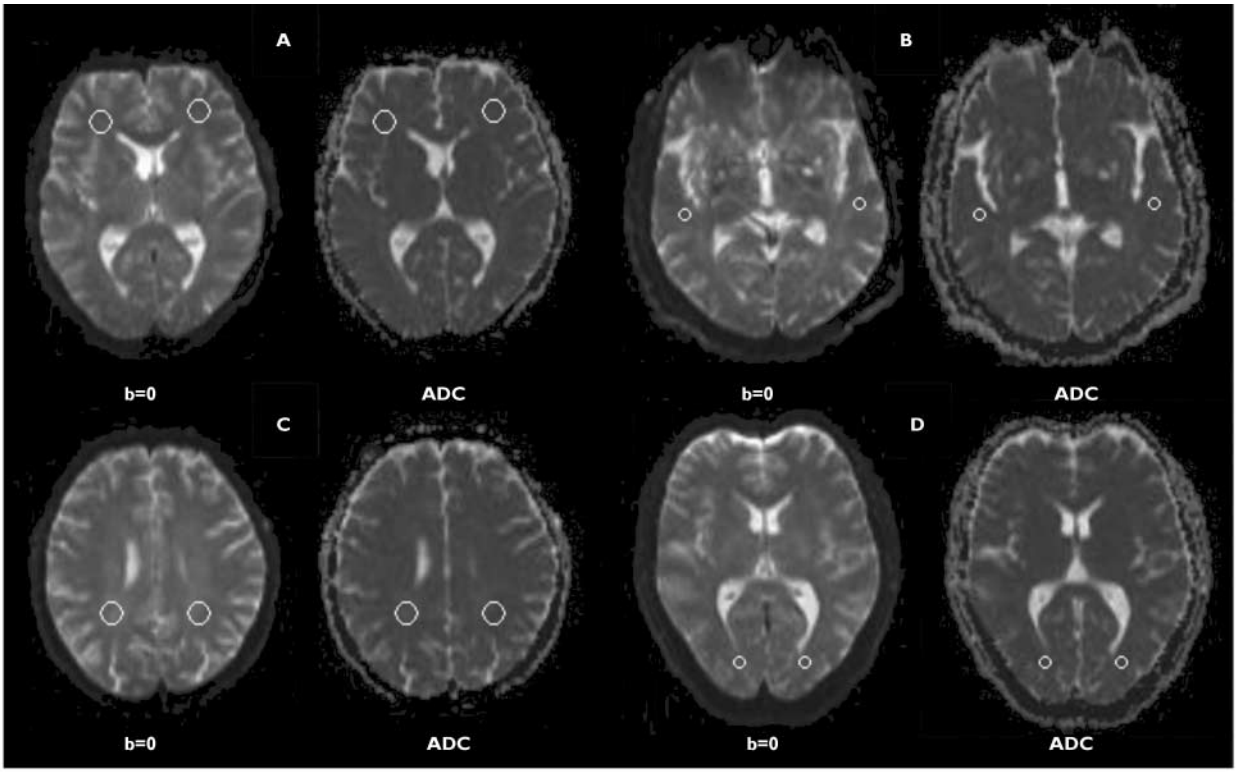

Fig. 1 Circular regions of interest were placed in cortical white matter on the *b*=0 echoplanar images, and then automatically transferred to apparent diffusion coefficient (ADC) maps (A, frontal lobes; B, temporal lobes; C, parietal lobes; D, occipital lobes).

raters (N.A. and A.V.) trace ten training scans were higher than 0.90.

Anatomical landmarks

Frontal cortex

Regions of interest were positioned in the axial slice at the level of the genu of corpus callosum (standardised at 43.5 mm^2), then in the inferior slice (standardised at 43.5 mm^2) and in the two superior slices (standardised at 84.4mm^2), posteriorly and medially to the frontal horns of the lateral ventricles.

Parietal cortex

Regions of interest (standardised at 84.4 mm^2) were placed in the axial slice when the lateral ventricles first disappeared and in the superior slice, posteriorly to the postcentral sulcus.

Temporal cortex

Regions of interest (standardised at 43.5 mm^2) were positioned in the axial slice at the level of the lateral fissure and in the inferior slice, posteriorly and laterally to the lateral fissure.

Occipital cortex

Regions of interest (standardised 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 Statistical Package for the Social Sciences version 11.0 for Windows and the two-tailed statistical significance level was set at $P<0.05$. Analysis of covariance (ANCOVA) with age and gender as covariates was performed to compare white-matter ADCs between the schizophrenia group and the control group. Pearson's correlation and partial correlation analyses controlled for age were used to examine possible association between age and clinical variables respectively, and ADC measures.

RESULTS

Compared with the control group, the participants with schizophrenia had significantly greater apparent diffusion coefficients for frontal, temporal and occipital white matter (Table 2), even when taking educational level into consideration (right and left frontal ADCs, $P=0.09$, $P=0.12$; right and left temporal ADCs, $P=0.006$, $P=0.009$; right and left occipital ADCs, $P=0.006$, $P=0.002$, respectively; ANCOVA, age, gender and educational level as covariates). Similar results were found when the schizophrenia group was compared separately with control participants recruited from hospital and university staff ($n=33$) (left frontal ADCs, $P=0.14$; temporal ADCs: $P<0.001$, occipital ADCs, $P<0.003$) and with control participants who had been treated for dizziness ($n=31$) (right frontal ADCs, $P=0.07$; temporal ADCs, $P=0.01$; occipital ADCs, $P\leqslant 0.01$) (ANCOVA; age and gender as covariates). Also, no significant difference for any ADC measure was found between the two control subgroups (ANCOVA; age and gender as covariates, $P>0.05$).

The ADC measures were still greater in the schizophrenia group than in the combined control group when both groups were stratified by gender, both in men (left frontal ADCs, $P=0.04$; temporal ADCs, $P<0.001$, occipital ADCs, $P<0.002$) and women (right temporal ADCs, $P=0.12$; left

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Table 2 Apparent diffusion coefficient measures for cortical white matter.

	ADC, 10^{-5} mm^2/s: mean (s.d.)			
	Control group (n=64)	Schizophrenia group (n=68)	F	P
Right frontal cortex	75.31 (3.43)	76.48 (4.34)	2.98	0.08
Left frontal cortex	72.17 (3.86)	73.59 (4.89)	4.10	0.04
Right temporal cortex	75.20 (4.37)	78.71 (5.66)	15.91	<0.001
Left temporal cortex	75.23 (4.67)	78.88 (5.63)	16.83	<0.001
Right parietal cortex	71.04 (4.52)	70.63 (3.80)	0.22	0.64
Left parietal cortex	72.86 (3.95)	73.27 (3.27)	0.60	0.44
Right occipital cortex	77.47 (4.43)	80.94 (6.37)	12.98	<0.001
Left occipital cortex	75.91 (3.70)	79.26 (5.14)	17.71	<0.001

ADC, apparent diffusion coefficient.

temporal ADCs, P=0.03; right occipital ADCs, P=0.06; left occipital ADCs, P=0.01) (Mann–Whitney U-test).

Age was significantly and directly correlated with left temporal ADC measures in the control group (r=0.28, P=0.02) but not in the schizophrenia group (r=0.16, P=0.18). No significant association was shown between age and other ADC values (Pearson's correlation, $P>0.05$) or between clinical variables (age at onset, length of illness, number of hospitalisations, BPRS scores, antipsychotic lifetime treatment) and white matter ADCs (partial correlation controlled for age, $P>0.05$). Furthermore, no significant difference for any ADC value was observed between patients treated with typical antipsychotic drugs (n=22) and those treated with atypical antipsychotics (n=44) (Mann–Whitney U-test, $P>0.05$). Also, patients with severe illness (BPRS>41; n=37) did not differ significantly on any ADC measure compared with patients with mild-to-moderate illness (BPRS$\leqslant$41; n=31) (Mann–Whitney U-test, $P>0.05$). A BPRS total score of 41 was chosen as the cut-off level for mild or moderate illness, indicated by Leucht *et al* (2005).

DISCUSSION

This study found widespread regional white-matter disruption in schizophrenia, as shown by higher ADCs in frontal, temporal and occipital lobes. To our knowledge, this is the largest study to show disrupted white-matter cytoarchitecture in schizophrenia (Kanaan *et al*, 2005). Consistently, impairments of cortical white-matter integrity have been found in people with schizophrenia by a number of prior small diffusion imaging studies (Kubicki *et al*, 2007, see online Table DS1). Specifically, abnormally increased water diffusion coefficients or abnormally decreased fractional anisotropy have been found in at least ten prior investigations of frontal lobes (Buchsbaum *et al*, 1998; Ardekani *et al*, 2003; Minami *et al*, 2003; Kumra *et al*, 2004; Wang *et al*, 2004; Kitamura *et al*, 2005; Kubicki *et al*, 2005*a*; Szeszko *et al*, 2005; Hao *et al*, 2006; Shin *et al*, 2006) and in temporo-occipital lobes (Lim *et al*, 1999; Agartz *et al*, 2001; Ardekani *et al*, 2003, 2005; Minami *et al*, 2003; Kumra *et al*, 2004; Kubicki *et al*, 2005*a*; Szeszko *et al*, 2005; Hao *et al*, 2006; Shin *et al*, 2006). However, some studies report preserved integrity of white matter in schizophrenia (Steel *et al*, 2001; Foong *et al*, 2002; Kubicki *et al*, 2002). Both ADC and fractional anisotropy are considered as complementary indices of white-matter microstructure organisation, providing evidence of disruption when increased and decreased respectively (Taylor *et al*, 2004). In our study, we did not report fractional ansotropy because the diffusion tensor sequence was not collected. Specifically, the ADC image provides a relative presentation of the diffusion coefficient in each pixel within the image, where low and high intensity values indicate respectively low and high diffusion (Basser, 2002). Abnormalities in cortical white matter may lead to impaired connection, which may ultimately alter the speed, quantity and/or quality of intrahemispheric communication, relevant to cognitive disturbances reported in schizophrenia (Krabbendam *et al*, 2005). This may be a result of reduced axonal density or myelination. Indeed, oligodendrocytes, which have the potential to influence myelination and synaptic transmission, have been found to be functionally abnormal in schizophrenia (Hof *et al*, 2002; Davis *et al*, 2003; Bartzokis & Altshuler, 2005). None the less, several factors may contribute to explain increased water white-matter diffusion, such as less dense packing of fibres, disruption of internal axonal integrity (reduced intra-axonal microtubular density), reduced degree of myelination or variation in membrane permeability to water. However, since white-matter is mostly composed of myelinated axons, the density of axonal membranes and myelin seem to play the major part (Beaulieu & Allen, 1994; Giedd, 2004).

Several earlier diffusion imaging studies reported frontal, temporal and occipital white-matter alterations within regions of interest identified by visual inspection of the individual anatomy, as in our method (Steel *et al*, 2001; Hoptman *et al*, 2002; Minami *et al*, 2003; Wolkin *et al*, 2003; Kumra *et al*, 2004; Kitamura *et al*, 2005). In particular, we examined the middle and inferior frontal white-matter regions, which have been shown to be functionally altered in schizophrenia (Shenton *et al*, 2001), potentially sustaining executive function deficits (MacDonald *et al*, 2005; Brambilla *et al*, 2007). Moreover, temporal regions of interest were positioned in the medial temporal white matter regions, which are involved in modulating language domain in humans and are likely to have a key role in language abnormalities in schizophrenia (Seidman *et al*, 2003; Antonova *et al*, 2004). Finally, the occipital regions of interest were placed in medial occipital areas, which have been shown to be altered in schizophrenia by other diffusion imaging studies (Lim *et al*, 1999; Agartz *et al*, 2001; Ardekani *et al*, 2003, 2005; Minami *et al*, 2003; Kumra *et al*, 2004). Furthermore, abnormalities in early-stage visual processing in schizophrenia have recently been shown, possibly contributing to higher-level cognitive deficits (Butler *et al*, 2005; Schechter *et al*, 2005). Therefore, our findings suggest that frontal and temporo-occipital white-matter disruption may in part support cognitive and language deficits in schizophrenia.

Taken together, these brain imaging findings indicate that cortical white-matter microstructure is disrupted in schizophrenia. Moreover, these results may be supported

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by post-mortem studies showing a quantitative reduction in white matter cells (Akbarian *et al*, 1996; Uranova *et al*, 2004). In particular, reduced expression of myelin and oligodendrocyte-related genes and proteins has been shown in schizophrenia, suggesting oligodendrocyte dysfunction (Flynn *et al*, 2003; Hof *et al*, 2003; Tkachev *et al*, 2003; Chambers & Perrone-Bizzozero, 2004). Specifically, neuregulin 1 (*NRG1*), a candidate gene for schizophrenia (Stefansson *et al*, 2002; Tosato *et al*, 2005; Williams *et al*, 2005), has been shown to have a key role in oligodendrocyte development and proliferation (Marchionni *et al*, 1993; Vartanian *et al*, 1999; Liu *et al*, 2001). Therefore, altered expression of *NRG1* or other myelination-related genes may potentially result in abnormal oligodendrocyte function or myelination in schizophrenia (Hakak *et al*, 2001; O'Donovan *et al*, 2003). However, it remains to be elucidated whether cortical white-matter impairment mostly reflects brain maldevelopment or neurodegeneration. In particular, it would be of great interest to understand how and when the white-matter disruption in schizophrenia relates to the physiological processes of white-matter maturation (Bartzokis, 2002; Hafner, 2004; Harrison, 2004; Bresnahan *et al*, 2005). Indeed, recent reports suggest that intracortical myelination increases during adulthood, reaching its peak during the fifth decade of life, particularly in the frontal and temporal lobes (Bartzokis *et al*, 2003), in a constant state of well-regulated structural and functional change. Affected myelination in schizophrenia, which may itself be due to multiple genetic and environmental factors, may contribute to alter this temporally expanded view of brain white-matter development from adolescence until middle age. As proposed by Bartzokis, this would ultimately result in dysregulation of the temporal synchronous development of widely distributed neural networks in schizophrenia, being manifested in the heterogeneity of symptoms and cognitive impairments (Bartzokis, 2002). Interestingly, white-matter alterations (particularly of corpus callosum) and abnormal downregulation of oligodendrocyte and myelination genes have been demonstrated in bipolar affective disorder as well as in schizophrenia (Brambilla *et al*, 2003, 2004; Tkachev *et al*, 2003). This sustains the notion that the two disorders may have similar white-matter pathophysiological pathways. Future brain imaging studies together with genetic investigations should further explore white-matter integrity and genes encoding myelin-related protein expression in people with first-episode schizophrenia and possibly bipolar affective disorder, and in the populations at high risk of developing these disorders.

Interestingly, we found a significant direct correlation between age and left temporal ADC values in the control group which was not present in the schizophrenia group. This is consistent with a recent investigation showing in controls, but not in patients, a significant negative effect of age on the integrity of the left superior longitudinal fasciculus, which connects the frontal and temporal cortex (Jones *et al*, 2006). Also, age-related decline of cerebral white-matter coherence in humans, which may represent subtle structural white-matter changes with normal ageing, has been demonstrated by diffusion imaging studies (Engelter *et al*, 2000; Pfefferbaum *et al*, 2000; O'Sullivan *et al*, 2001; Sullivan *et al*, 2001). Thus, as a speculative interpretation, it is possible that the effects of physiological ageing on white matter cannot be seen in schizophrenia owing to the presence, since early adolescence, of abnormal neurodevelopment and cytoarchitectural organisation of cortical white matter, particularly in the temporal region (Pantelis *et al*, 2005).

No significant association between ADC values and any clinical variable was found in our study, consistent with several prior reports exploring correlations between diffusion measures and clinical features in schizophrenia (Steel *et al*, 2001; Kumra *et al*, 2004, 2005; Jones *et al*, 2005; Kubicki *et al*, 2005*a*; Kitamura *et al*, 2005; Szeszko *et al*, 2005). This suggests that cortical white-matter disruption in schizophrenia is not a secondary effect of chronicity, medication or psychopathology but is potentially related to the core pathophysiology of the disease. However, it should be mentioned that two small studies have found increased white-matter alterations in people with schizophrenia with more severe negative symptoms in the right insula (Shin *et al*, 2006) and the inferior frontal region (Wolkin *et al*, 2003). However, the latter group also showed a relationship between impulsivity/aggression and altered white-matter microstructure in the right inferior frontal region and insula in men with schizophrenia (Hoptman *et al*, 2002, 2004). Therefore, the correlation between white-matter cytoarchitecture and clinical symptoms in schizophrenia is still controversial and needs further investigation in large samples.

It should be noted that our schizophrenia sample mostly comprised treated patients with chronic illness, thus it is not clear whether white-matter disruption preceded the onset of the illness or appeared subsequently as a result of illness course or psychotropic treatment. However, length of illness or antipsychotic lifetime administration did not significantly affect ADC values, suggesting that cortical white-matter abnormalities may not be related to illness or medication. Also, we recruited a relatively larger number of participants than prior diffusion imaging studies, with a good match between those in the schizophrenia and control groups, providing adequate power. Part of our control group was selected from individuals undergoing MRI scanning for dizziness, which may represent a methodological limitation. However, these participants were fully recovered at the time of scanning and had no evidence of central nervous system abnormalities on the scan. Finally, no particular white-matter tracts could be detected with our approach, such as the uncinate or the arcuate fasciculi which form specific temporo- and parieto-frontal connections (Burns *et al*, 2003; Kubicki *et al*, 2005*b*; Jones *et al*, 2006).

In conclusion, altered cortical white-matter microstructure in schizophrenia has been replicated in this large study, particularly in frontal and temporo-occipital lobes. Hypothetically, abnormal myelination due to oligodendrocyte dysfunction might account for these findings. This might potentially affect intrahemispheric communication and ultimately lead to the cognitive disturbances seen in people with schizophrenia.

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