Psychological Medicine (2013), **43**, 2301–2309. © Cambridge University Press 2013
doi:10.1017/S0033291713000238

ORIGINAL ARTICLE

White-matter microstructure in previously drug-naive patients with schizophrenia after 6 weeks of treatment

Q. Wang[1,2], C. Cheung[3], W. Deng[1,2], M. Li[1], C. Huang[1], X. Ma[1,2], Y. Wang[1,2], L. Jiang[1], P. C. Sham[3], D. A. Collier[4], Q. Gong[5], S. E. Chua[3], G. M. McAlonan[6]* and T. Li[1,2]*

[1] *Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, China*
[2] *State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan, China*
[3] *Department of Psychiatry, University of Hong Kong, Pokfulam, SAR China*
[4] *MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, UK*
[5] *Huaxi MR Research Centre, Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China*
[6] *Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College London, UK*

Background. It is not clear whether the progressive changes in brain microstructural deficits documented in previous longitudinal magnetic resonance imaging (MRI) studies might be due to the disease process or to other factors such as medication. It is important to explore the longitudinal alterations in white-matter (WM) microstructure in antipsychotic-naive patients with first-episode schizophrenia during the very early phase of treatment when relatively 'free' from chronicity.

Method. Thirty-five patients with first-episode schizophrenia and 22 healthy volunteers were recruited. High-resolution diffusion tensor imaging (DTI) was obtained from participants at baseline and after 6 weeks of treatment. A 'difference map' for each individual was calculated from the 6-week follow-up fractional anisotropy (FA) of DTI minus the baseline FA. Differences in Positive and Negative Syndrome Scale (PANSS) scores and Global Assessment of Functioning (GAF) scores between baseline and 6 weeks were also evaluated and expressed as a 6-week/baseline ratio.

Results. Compared to healthy controls, there was a significant decrease in absolute FA of WM around the bilateral anterior cingulate gyrus and the right anterior corona radiata of the frontal lobe in first-episode drug-naive patients with schizophrenia following 6 weeks of treatment. Clinical symptoms improved during this period but the change in FA did not correlate with the changes in clinical symptoms or the dose of antipsychotic medication.

Conclusions. During the early phase of treatment, there is an acute reduction in WM FA that may be due to the effects of antipsychotic medications. However, it is not possible to entirely exclude the effects of underlying progression of illness.

Received 24 February 2012; Revised 6 November 2012; Accepted 24 January 2013; First published online 27 February 2013

Key words: First episode, longitudinal study, microstructural deficits, schizophrenia.

Introduction

Schizophrenia is a common and serious mental illness that affects 1% of the population worldwide. It remains the leading cause of mental disability among young adults and is typically associated with structural (Ho *et al.* 2006; Bora *et al.* 2011) and functional abnormalities (Callicott *et al.* 2003; Lui *et al.* 2009) of the brain. It has been suggested that the pathophysiology of schizophrenia may lie in abnormal interactions or dysconnectivity across a distributed network of brain regions (Stephan *et al.* 2006; Segal *et al.* 2007). Consistent with this, cross-sectional studies have shown the presence of structural brain abnormalities in the early phase of schizophrenic illness (Federspiel *et al.* 2006; Kanaan *et al.* 2006; Peters *et al.* 2010; Wang *et al.* 2011), although several studies failed to detect structural brain anomalies in early-episode patients (Moncrieff & Leo, 2010). More extensive structural brain abnormalities were found in chronic patients with schizophrenia, which may reflect the progressive nature of this condition (Chan *et al.* 2011). However, the abnormalities found in chronic patients may be influenced by several factors, particularly medication effects, that are difficult to disentangle from disease progression (Bora *et al.* 2011).

Clinical observations and empirical studies have demonstrated that antipsychotic medications bring

* Author for correspondence: Professor T. Li, Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China.
(Email: xuntao26@hotmail.com) [T. Li]
(Email: grainne.mcalonan@kcl.ac.uk) [G. McAlonan]

both benefits and side-effects to schizophrenic patients (Lewis, 2011). Although the majority of patients benefit from the reduction of positive symptoms after antipsychotic treatment, many continue to have negative symptoms, neurocognitive impairments and progressive brain tissue abnormalities (Lieberman *et al.* 2005; van Haren *et al.* 2007; Cahn *et al.* 2009; Olabi *et al.* 2011). However, previous studies using morphometric magnetic resonance imaging (MRI) to examine the effects of antipsychotics on cortical grey matter (GM) and white matter (WM) have yielded ambiguous results (McCormick *et al.* 2005; Pressler *et al.* 2005). In a systematic review, Navari & Dazzan (2009) found that antipsychotic medication acted regionally rather than globally on the brain. Because it is problematic to distinguish between the effects of medication and pathogenesis in cross-sectional studies, longitudinal designs have been used to partly overcome this difficulty. In a long-term longitudinal study of 211 patients over a 7–14-year follow-up period, Ho *et al.* (2011) found that antipsychotics have a subtle but measurable influence on brain tissue losses over time, although volumetric changes do not seem to be related to the dose of antipsychotics (Hulshoff Pol & Kahn, 2008). In addition, studies on experimental animals supplement evidence that antipsychotic medications cause a reduction in brain volume (Dorph-Petersen *et al.* 2005; Konopaske *et al.* 2007, 2008).

The extent to which progressive structural brain changes are a consequence of disease or are at least partly caused by antipsychotic medication is of fundamental importance (Olabi *et al.* 2011). The majority of longitudinal studies of schizophrenia have focused on macrostructural indices of volume changes in GM and WM (Koutsouleris *et al.* 2010; Ho *et al.* 2011; Olabi *et al.* 2011). However, these approaches are limited both in terms of localizing WM 'networks' affected and probing acute microstructural changes. By contrast, diffusion tensor imaging (DTI) provides a useful tool for assessing WM structural integrity and connectivity *in vivo*. It yields a series of quantitative measures, including fractional anisotropy (FA), that reflect the integrity of WM tracts. Lower FA values have been reported in many parts of the principal WM bundles in schizophrenia, although there are differences in the locations implicated across studies (Ardekani *et al.* 2003; Kubicki *et al.* 2003; Wang *et al.* 2004). Combined volumetric MRI and DTI analyses suggest that FA decline precedes WM volume loss and DTI indices may therefore be more sensitive to WM structural changes in schizophrenia (Hugenschmidt *et al.* 2008; Bora *et al.* 2011). Unfortunately, few studies have focused on the effects of antipsychotic medication on DTI measures. Cross-sectional studies have reported no significant differences in DTI measures between age-matched chronic and briefly medicated patients, nor any correlation between FA values and the duration of illness (Peters *et al.* 2008, 2010; Kanaan *et al.* 2009*a*, *b*). However, to assess the impact of antipsychotics on WM microstructure directly, longitudinal investigations are needed, preferably in the early stage of illness, which is free from confounds of chronicity.

Therefore, in the present study, we performed a DTI analysis of WM microstructural changes in a cohort of first-episode, drug-naive patients with schizophrenia before and after 6 weeks of treatment with standard antipsychotic medication. A matched healthy control group was included. We tested the hypothesis that patients with first-episode schizophrenia would have changes in WM microstructure in the early phase of illness within 6 weeks of treatment. We also conducted an exploratory analysis to determine whether changes in WM microstructure would be related to acute outcome in terms of changes in clinical symptoms.

Method

Participants and clinical assessments

Forty out-patients and in-patients were initially enrolled in an ongoing longitudinal study in the Mental Health Centre in West China Hospital of Sichuan University. All patients were experiencing their first episode of psychosis and were drug-naive when recruited to the study. They were assessed by one of two trained psychiatrists using the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-I/P), and were found to fulfil the diagnostic criteria for schizophrenia or schizophreniform psychosis as described in DSM-IV. Among the 40 patients, three diagnosed with schizophreniform psychosis were followed up for at least 6 months and confirmed to meet the DSM-IV diagnosis criteria for schizophrenia. Twenty-three healthy controls were recruited from the local area by poster advertisement. All healthy controls were screened for the lifetime absence of psychiatric illnesses by using the SCID, Non-Patient Edition (SCID-I/NP) and were interviewed to ascertain that there was no psychiatric illness in their first-degree relatives. Participants with evidence of organic brain disorders, alcohol or drug abuse, pregnancy or any other serious medical condition, such as brain tumour or epilepsy, were excluded from the study. The 6-week time period was selected as an early phase to evaluate the impact of antipsychotic treatment relatively free from confounds of chronicity (Chua *et al.* 2009; Deng *et al.* 2009; Lui *et al.* 2010). Before the patients started any antipsychotic treatment, they underwent assessment of psychopathology and function by an experienced psychiatrist using the Positive and Negative

https://doi.org/10.1017/S0033291713000238 Published online by Cambridge University Press

Syndrome Scale (PANSS; Kay *et al.* 1987) and the Global Assessment of Functioning (GAF; Goldman *et al.* 1992) respectively. All patients and controls then had MRI brain scans at baseline. After 6 weeks of treatment, an MRI scan was scheduled again for both patients and healthy controls after quality controls. All patients were assessed with the PANSS and the GAF to evaluate changes in clinical symptoms and global functions after the 6 weeks of treatment. The duration of illness was measured from the onset of the first psychiatric symptoms to the first assessment.

In the present study, patients with schizophrenia received antipsychotic medication according to the case-clinician's preference. Seventeen patients were treated with risperidone, six with olanzapine, six with quetiapine, three with sulpiride, two with aripiprazole and one with haloperidol (Table 1).

All participants were Han Chinese and right-handed. The handedness of the participants was assessed with the Annett Hand Preference Questionnaire (AHPQ; Annett, 1970). This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Broad (IRB) of West China Hospital, Sichuan University. After a careful description the study, written informed consent was obtained from all participants.

MRI scans

All participants underwent MRI scanning in the Department of Radiology at West China Hospital using a Signa 3-T scanner (GE Medical Systems, USA) with an eight-channel phased-array head coil. In the MRI unit, the usual practice to ensure MRI image quality assurance is based on an in-house protocol in which phantoms are used to measure the signal-to-noise ratio (SNR) and image uniformity on a daily basis, noting the voltage of the transmitting radio frequency amplifier. High-resolution DTI data were acquired by using a single-shot spin echo–planar imaging (EPI) sequence [repetition time/echo time (TR/TE)=10 000/70.8 ms, 3-mm axial slices with no gap, matrix=256×256, field of view (FOV)=24×24 cm^2, acquisition time=5 min 40 s]. The DTI sequence used in this protocol included 15 diffusion gradient directions [b=1000 s/mm^2, number of excitations (NEX)=2] and 1 volume without diffusion weighting (b=0, NEX=2) for 42 slices throughout the whole brain. Anatomical three-dimensional spoiled gradient recalled (3D-SPGR) T1 data were also acquired for registration purposes [TR/TE=8.5/3.4 ms, 1-mm axial slices, matrix=512×512, FOV=24 cm^2, inversion time (TI)=400 ms, NEX=1]. An experienced neuroradiologist reviewed all scans to exclude obvious gross abnormalities.

Table 1. *Dose for each antipsychotic medication in different patients*

	Risperidone	Olanzapine	Quetiapine	Aripiprazole	Sulpiride	Haloperidol
No. of patients	17	6	6	2	3	1
Cumulative dosage (mg), mean (S.D.)	191.52 (50.82)	695.52 (362.04)	25 899.72 (9360.12)	1069.32 (564.06)	34 999.86 (6415.5)	672 (–)
CPZ equivalents (mg), mean (S.D.)	9720.9 (2496.9)	9297.12 (7228.62)	34 532.82 (12 480.3)	14 254.8 (7519.68)	17 500.14 (3207.96)	33 600 (–)

CPZ, Chlorpromazine; S.D., standard deviation.

https://doi.org/10.1017/S0033291713000238 Published online by Cambridge University Press

Image processing

Images were processed and analysed using SPM8 software (www.fil.ion.ucl.ac.uk/spm/software/spm8/). FA maps were generated from each participant's DTI scan using the freely available DTIstudio software (http://cmrm.med.jhmi.edu/). Prior to FA calculation, the DTI scans were realigned using the built-in function in DTIstudio so that each DTI image (b=0 s/mm^2) could be corrected for motion. Three participants with schizophrenia and one healthy control were excluded from this study because of head and body motion in the baseline MRI scan and two patients were excluded from later analysis because of unsatisfactory image data in the follow-up MRI scan. Finally, this study included 35 patients and 22 healthy controls who had completed both baseline and follow-up experiments. All 3D-SPGR images were corrected for inhomogeneity, normalized, and segmented using an integrated generative model (unified segmentation) with default parameters applied. The DTI dataset was registered with the anatomical T1 images by mutual information co-registration between the b=0 image and the T1 image. The normalization parameter of the T1 image was used to normalize the FA map to standard space. Furthermore, each subject's image at week 6 was first registered to the baseline image using a rigid body transformation and then mapped to the baseline image using a high-dimensional deformation. This yielded a follow-up image in the space of the baseline image, but with FA values reflecting the follow-up image. The normalized FA maps were resliced to 2 mm × 2 mm × 2 mm and smoothed with a 6-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel (Wang *et al.* 2011). An explicit mask for statistical analysis was created by averaging the WM mask of all subjects at a threshold of 0.2 (SPM Masking Toolbox).

Statistical analyses

First, clinical symptom scores (positive, negative and general psychopathological symptoms) and GAF scores were compared at both baseline and after 6 weeks using a repeated-measures MANOVA with gender as a covariate. Correlations between changes in symptom score and changes in FA were further examined only if there was a significant difference in symptom scores between the two time points. Second, a 'difference map' for each individual was calculated from the 6-week follow-up FA of DTI minus the baseline FA, which reflected the changes in the FA values between the two time points. These difference maps were then compared between cases and controls. Third, we conducted partial correlation analyses to determine whether changes in WM FA were dose dependent or related to symptom changes post-treatment, or whether duration of illness prior to treatment influenced the extent of acute changes post-treatment. The difference in PANSS scores and GAF scores between baseline and the 6-week follow-up was expressed as a ratio of the scores at follow-up and baseline, that is the 'PANSS reduction ratio' and the 'GAF improvement ratio' respectively. The significance level was set with a voxel-level threshold of p<0.05, after family-wise error correction for multiple comparisons, and an extent threshold of p<0.05 (uncorrected), with a minimum cluster size of 50 voxels. In all these analyses, gender was included as a covariate when appropriate. The FA values of each difference map were extracted for subsequent analyses and all correlation analyses were performed using SPSS version 12.0 (SPSS Inc., USA).

Results

Demographic characteristics

The demographic characteristics of the participants are shown in Table 2. There were no significant differences in age (t_{55}=−0.80, p>0.429), years of education (t_{242}=0.54, p<0.595) and gender ratio (χ^2_1=0.19, p<0.276) between the patients and controls.

Comparison between cases and controls at baseline

As shown in Fig. 1, compared to healthy controls, there was a significant decrease in the absolute FA value in WM around the right posterior cingulate gyrus (x=14, y=−42, z=29, p=1.13×10^{-4}), and this cluster was seen to extend to the right anterior corona radiata and the precentral gyrus of the frontal lobe (x=40, y=−2, z=28, p=1.75×10^{-4}) in first-episode drug-naive patients with schizophrenia at baseline.

Longitudinal comparisons of clinical symptoms and GAF between baseline and week 6

In the repeated-measures MANOVA, there were significant differences in positive, general psychopathological symptoms and GAF scores between baseline and the 6-week follow-up time point (F=141.66, p<0.001; F=33.00, p<0.003; F=102.52, p<0.001 respectively). No significant difference was evident in negative symptoms between the two time points (F=3.05, p<0.091), and therefore negative symptom measures were not analysed further.

Absolute changes in FA values after 6 weeks of antipsychotic treatment

As shown in Fig. 2, compared to healthy controls, there was a significant decrease in absolute FA values in

https://doi.org/10.1017/S0033291713000238 Published online by Cambridge University Press

Table 2. *Demographic and clinical characteristics of healthy controls and participants with schizophrenia for baseline and follow-up data*

		Case			
	Control	Baseline	Week 6	$t/\chi^2/F$	p
n	22	35			
Age (years), mean (S.D.)	22.41 (5.96)	23.84 (6.96)		−0.80	0.429
Educational attainment (years), mean (S.D.)	12.84 (3.41)	12.37 (3.11)		0.54	0.595
Age range (years)	16–39	16–41			
Gender (M/F)	14/8	16/19		0.19	0.276
Age at onset (years), mean (S.D.)		23.39 (7.20)			
Duration of illness (months), mean (S.D.)		7.26 (5.32)			
PANSS score, mean (S.D.)					
Positive symptoms		27.46 (6.08)	14.06 (4.08)	141.66	0.001
Negative symptoms		18.83 (7.04)	16.73 (4.35)	3.05	0.091
General psychopathological symptoms		49.03 (8.26)	33.80 (9.29)	33.00	0.003
GAF score, mean (S.D.)		26.71 (7.46)	53.83 (14.64)	102.52	0.001

M, Male; F, female; PANSS, Positive and Negative Symptoms Scale; GAF, Global Assessment of Functioning; S.D., standard deviation.

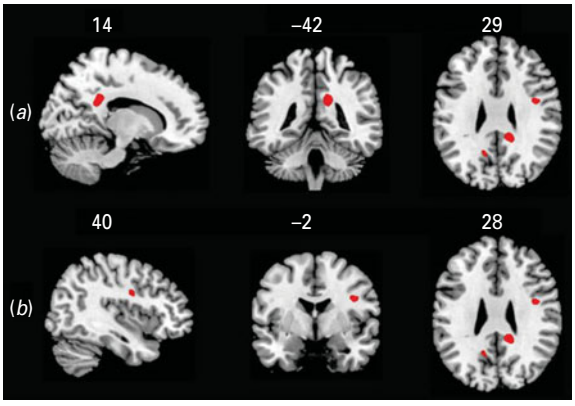

Fig. 1. Comparsion between cases and controls at baseline. Compared to healthy controls, patients with schizophrenia had significant reduction in absolute fractional anisotropy (FA) values at baseline in white matter around the right posterior cingulate gyrus (x=14, y=−42, z=29, $p=1.13\times10^{-4}$), and this cluster seemed to extend to the right anterior corona radiata and the precentral gyrus of the frontal lobe (x=40, y=−2, z=28, $p=1.75\times10^{-4}$).

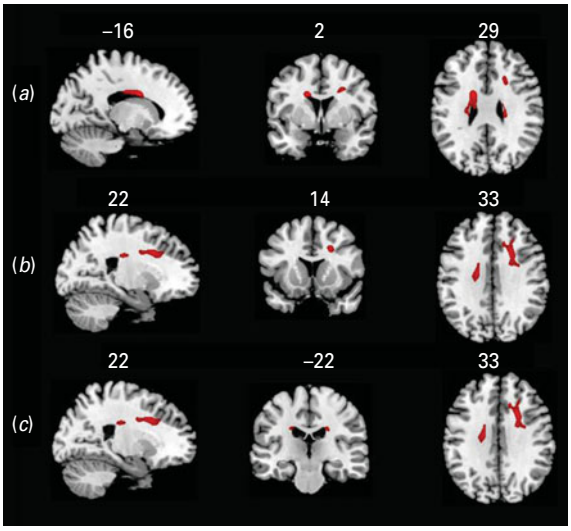

Fig. 2. Comparison of difference maps between patients and controls. Compared to healthy controls, patients with schizophrenia had a significant reduction in absolute fractional anisotropy (FA) values following 6 weeks of antipsychotic treatment in the bilateral anterior cingulate gyrus and the right anterior corona radiata of the frontal lobe (x=−16, y=2, z=29, $p=0.01$, voxels=1332; x=22, y=14, z=33, $p=0.001$, voxels=1617; and x=22, y=−22, z=33, voxels=685 respectively).

WM around the bilateral anterior cingulate gyrus and the right anterior corona radiata of the frontal lobe in first-episode drug-naive patients with schizophrenia following 6 weeks of treatment. The cluster in the right anterior cingulate region seemed to extend into the right frontal lobe (Fig. 2). Compared with baseline, the mean FA values at week 6, which were extracted from WM bundles of the bilateral anterior cingulate gyrus and the right anterior corona radiata of the frontal lobe (x=−16, y=2, z=29, $p=0.01$; x=22, y=14, z=33, $p=0.001$; and x=22, y=−22, z=33, voxels=685 respectively), decreased to about 8.45, 7.82 and 4.96% respectively. By contrast, the corresponding percentage decreases in the controls were 1.03, 0.895 and 0.015% respectively and these percentage decreases were significantly different between cases and controls.

https://doi.org/10.1017/S0033291713000238 Published online by Cambridge University Press

Correlation of change in FA value with changes in symptom scores, duration of illness, GAF score and antipsychotics dosages

There were no significant correlations between the change in FA value and the improvement in clinical symptoms, positive (r=0.195, p=0.277, df=31), general psychopathological symptoms (r=0.214, p=0.233, df=31), and GAF score (r=0.040, p=0.826, df=31) after 6 weeks of treatment. Moreover, there were no significant correlations between change in FA value and duration of illness (r=0.097, p=0.592, df=31) or between the change in FA value and the dose of antipsychotic medications (r=−0.208, p=0.246, df=31) after the 6 weeks of treatment. Thus, WM FA changes were dose independent and not linked to symptom changes. In addition, duration of illness did not influence vulnerability to acute changes in WM FA following drug treatment.

Discussion

In the present study we found a progressive change in WM microstructure around the bilateral anterior cingulate gyrus and the right anterior corona radiata of the frontal lobe in first-episode drug-naive patients with schizophrenia at 6 weeks of follow-up. Non-specific changes were controlled for by including a cohort of healthy controls scanned within the same follow-up period (6 weeks). During this period we found that the negative symptoms of the patients with schizophrenia remained stable whereas their positive and general psychopathological symptoms improved significantly. However, the WM FA changes did not correlate with symptom improvement, short-term outcomes or the dose of antipsychotic medication. Moreover, the duration of illness prior to treatment did not influence vulnerability to WM changes post-treatment.

Although are several possible explanations for the acute alteration in WM microstructure in patients with schizophrenia, antipsychotic medication is likely to be the major factor. Studies of the effects of antipsychotic medication on DTI measurements have generally found no relationship between FA values and dose of antipsychotic medications (Kanaan *et al.* 2009*a*; Peters *et al.* 2009; White *et al.* 2011), although small sample sizes and lack of long-term longitudinal designs have constrained interpretation. Our study, however, confirmed that the effect of antipsychotic medications on WM microstructure within 6 weeks is not dose dependent. Although we cannot rule out the possibility of disease progression in our findings, during the 'short' 6-week follow-up period the positive symptoms of schizophrenia improved whereas the negative symptoms remained stable. Thus, there was no evidence of symptomatic progression of disease in our patients. This suggests that the reduction in FA elicited by antipsychotic medication is not related to clinical presentation in a straightforward manner.

We acknowledge the challenge in labelling the directionality of any neuroimaging findings as 'beneficial' or 'harmful'. As regional WM FA has consistently been reported to be lower in schizophrenia compared to typical control groups (Wang *et al.* 2004, 2011; Cheung *et al.* 2011), lower FA in schizophrenia seems to be 'pathological'. We previously reported that FA in cingulate WM is significantly lower in patients compared to controls, even though patients with the lowest FA had the fewest positive symptoms (Cheung *et al.* 2011). The direction of the present findings is similar in that positive symptoms improved while FA decreased. Thus, we cautiously suggest that our findings indicate that although medications currently used to treat schizophrenia improve positive symptoms, they cannot arrest or reverse an injurious process occurring in the brain of patients with schizophrenia, and may even worsen WM pathology.

The abnormalities we observed in cingulate gyrus WM are in line with Rosenberger's (Rosenberger *et al.* 2008) and others' findings suggesting that this region is particularly vulnerable to damage in schizophrenia (Wang *et al.* 2004; Cheung *et al.* 2011). A potential toxic effect of antipsychotic medication might include oxidative stress and excitatory neurotoxicity and previous longitudinal studies have linked antipsychotic medications to brain tissue losses (Ho *et al.* 2011; Olabi *et al.* 2011). For example, Lieberman *et al.* (2005) suggested that haloperidol could explain GM losses during the first 12 weeks after first time of onset and Ho *et al.* (2003) observed similar progressive GM losses in the brains of schizophrenic patients during the initial year after diagnosis despite ongoing antipsychotic drug treatment. They also found that typical and atypical drugs had differential effects on brain volume (Ho *et al.* 2003). By contrast, in animal models, typical and atypical antipsychotic medications have been reported to have an equivalent and highly significant impact causing a decrease in brain volumes. For example, in the macaque, typical and atypical medications a decrease in weight and volume of fresh brain (Dorph-Petersen *et al.* 2005), and in the rat, haloperidol and olanzapine trigger comparable decreases in whole brain volume, driven mainly by frontal lobe volume reductions (Vernon *et al.* 2011). A common action of both atypical and typical antipsychotics is D2/D3 receptor blockade of D2/3, which in turn increases dopamine turnover. The latter may theoretically generate free radicals and lead to oxidative damage (Carlsson & Lindqvist, 1963), and on

https://doi.org/10.1017/S0033291713000238 Published online by Cambridge University Press

integrating our study with that of Ho *et al.* (2011), the evidence suggests that antipsychotic medications may have undesirable effects on brain structure. However, we balance this postulate with evidence that, in the acute phase of illness, antipsychotic medications improve positive symptoms and may 'reverse' the lower striatal volumes found in patients prior to drug treatment (Leung *et al.* 2011).

There are some limitations in our study. First, during the early phase of illness presumed abnormalities in WM microstructure and the level of neuronal pathology may be not extensive enough to be detected by DTI measures and may be too subtle to be correlated with clinical symptoms, outcome and drug dosages. To exclude such false negatives, longer follow-up time periods will be needed to explore long-term brain–behaviour–medication relationships. Second, although this is the largest 6-week DTI follow-up study in drug-naive patients pre- and post-treatment to date, the sample size may still lack power to fully link changes in outcome and clinical symptoms with subtle changes in WM. Again we may have false-negative results that perhaps obscure increases or normalization of FA that relate to good clinical outcomes. Third, it is possible that there are non-linear rather than linear relationships among the changes in microstructure, clinical symptoms, outcome and drug dosages. More advanced statistical approaches, such as random effect mixed models, may be preferable for the investigation of these complex relationships (Ho *et al.* 2011). Finally, as with any *in-vivo* MRI index, we cannot definitely conclude that the underlying pathological mechanism is responsible for the changes observed. Although FA is considered as a proxy index of microstructural organization, the effect of antipsychotic medications may also be indirect through altered blood flow or neuron metabolism in the brain.

In conclusion, our findings show that, during the early phase of treatment, there is an acute reduction in WM FA in the majority of patients with first-episode schizophrenia. The changes may be caused by antipsychotic medications. However, an underlying progression of the illness, despite the improvement in some clinical symptoms in the patients with schizophrenia, cannot be fully excluded.

Acknowledgements

This work was partly funded by the National Nature Science Foundation of China (81130024, 30530300 and 30125014, T.L.; 30971056, Q.W.), the National Basic Research Programme of China (973 Programme 2007CB512301, T.L.), the Ph.D. Programmes Foundation of the Ministry of Education of China (20110181110014, T.L.), the National Key Technology R&D Programme of the Ministry of Science and Technology of China during the 12th Five-Year Plan (2011BAZ02530, T.L.), a National Alliance for Research on Schizophrenia and Depression (NARSAD) Independent Investigator Award (T.L.), the Wellcome Trust (International Collaborative award to T.L. and D.A.C.), and the China Postdoctoral Science Foundation (20090461337 and 201003699, W.D.).

Declaration of Interest

None.

References

Annett M (1970). A classification of hand preference by association analysis. *British Journal of Psychology* **61**, 303–321.

Ardekani BA, Nierenberg J, Hoptman MJ, Javitt DC, Lim KO (2003). MRI study of white matter diffusion anisotropy in schizophrenia. *Neuroreport* **14**, 2025–2029.

Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, Yucel M, Velakoulis D, Pantelis C (2011). Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophrenia Research* **127**, 46–57.

Cahn W, Rais M, Stigter FP, van Haren NE, Caspers E, Hulshoff Pol HE, Xu Z, Schnack HG, Kahn RS (2009). Psychosis and brain volume changes during the first five years of schizophrenia. *European Neuropsychopharmacology* **19**, 147–151.

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR (2003). Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *American Journal of Psychiatry* **160**, 2209–2215.

Carlsson A, Lindqvist M (1963). Effect of chlorpromazine or haloperidol on formation of 3methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacologica et Toxicologica* **20**, 140–144.

Chan RC, Di X, McAlonan GM, Gong QY (2011). Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. *Schizophrenia Bulletin* **37**, 177–188.

Cheung V, Chiu CP, Law CW, Cheung C, Hui CL, Chan KK, Sham PC, Deng MY, Tai KS, Khong PL, McAlonan GM, Chua SE, Chen E (2011). Positive symptoms and white matter microstructure in never-medicated first episode schizophrenia. *Psychological Medicine* **41**, 1709–1719.

Chua SE, Deng Y, Chen EY, Law CW, Chiu CP, Cheung C, Wong JC, Lienenkaemper N, Cheung V, Suckling J, McAlonan GM (2009). Early striatal hypertrophy in first-episode psychosis within 3 weeks of initiating antipsychotic drug treatment. *Psychological Medicine* **39**, 793–800.

https://doi.org/10.1017/S0033291713000238 Published online by Cambridge University Press

Deng MY, McAlonan GM, Cheung C, Chiu CP, Law CW, Cheung V, Sham PC, Chen EY, Chua SE (2009). A naturalistic study of grey matter volume increase after early treatment in anti-psychotic naive, newly diagnosed schizophrenia. *Psychopharmacology* **206**, 437–446.

Dorph-Petersen KA, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA (2005). The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology* **30**, 1649–1661.

Federspiel A, Begre S, Kiefer C, Schroth G, Strik WK, Dierks T (2006). Alterations of white matter connectivity in first episode schizophrenia. *Neurobiology of Disease* **22**, 702–709.

Goldman HH, Skodol AE, Lave TR (1992). Revising axis V for DSM-IV: a review of measures of social functioning. *American Journal of Psychiatry* **149**, 1148–1156.

Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Archives of General Psychiatry* **60**, 585–594.

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011). Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry* **68**, 128–137.

Ho BC, Milev P, O'Leary DS, Librant A, Andreasen NC, Wassink TH (2006). Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. *Archives of General Psychiatry* **63**, 731–740.

Hugenschmidt CE, Peiffer AM, Kraft RA, Casanova R, Deibler AR, Burdette JH, Maldjian JA, Laurienti PJ (2008). Relating imaging indices of white matter integrity and volume in healthy older adults. *Cerebral Cortex* **18**, 433–442.

Hulshoff Pol HE, Kahn RS (2008). What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophrenia Bulletin* **34**, 354–366.

Kanaan R, Barker G, Brammer M, Giampietro V, Shergill S, Woolley J, Picchioni M, Toulopoulou T, McGuire P (2009*a*). White matter microstructure in schizophrenia: effects of disorder, duration and medication. *British Journal of Psychiatry* **194**, 236–242.

Kanaan RA, Borgwardt S, McGuire PK, Craig MC, Murphy DG, Picchioni M, Shergill SS, Jones DK, Catani M (2009*b*). Microstructural organization of cerebellar tracts in schizophrenia. *Biological Psychiatry* **66**, 1067–1069.

Kanaan RA, Shergill SS, Barker GJ, Catani M, Ng VW, Howard R, McGuire PK, Jones DK (2006). Tract-specific anisotropy measurements in diffusion tensor imaging. *Psychiatry Research* **146**, 73–82.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Konopaske GT, Dorph-Petersen KA, Pierri JN, Wu Q, Sampson AR, Lewis DA (2007). Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. *Neuropsychopharmacology* **32**, 1216–1223.

Konopaske GT, Dorph-Petersen KA, Sweet RA, Pierri JN, Zhang W, Sampson AR, Lewis DA (2008). Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. *Biological Psychiatry* **63**, 759–765.

Koutsouleris N, Gaser C, Bottlender R, Davatzikos C, Decker P, Jager M, Schmitt G, Reiser M, Moller HJ, Meisenzahl EM (2010). Use of neuroanatomical pattern regression to predict the structural brain dynamics of vulnerability and transition to psychosis. *Schizophrenia Research* **123**, 175–187.

Kubicki M, Westin CF, Nestor PG, Wible CG, Frumin M, Maier SE, Kikinis R, Jolesz FA, McCarley RW, Shenton ME (2003). Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Biological Psychiatry* **54**, 1171–1180.

Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q, Chua S, McAlonan G (2011). Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting. *Schizophrenia Bulletin* **37**, 199–211.

Lewis DA (2011). Antipsychotic medications and brain volume: do we have cause for concern? *Archives of General Psychiatry* **68**, 126–127.

Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M (2005). Antipsychotic drug effects on brain morphology in first-episode psychosis. *Archives of General Psychiatry* **62**, 361–370.

Lui S, Deng W, Huang X, Jiang L, Ma X, Chen H, Zhang T, Li X, Li D, Zou L, Tang H, Zhou XJ, Mechelli A, Collier DA, Sweeney JA, Li T, Gong Q (2009). Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. *American Journal of Psychiatry* **166**, 196–205.

Lui S, Li T, Deng W, Jiang L, Wu Q, Tang H, Yue Q, Huang X, Chan RC, Collier DA, Meda SA, Pearlson G, Mechelli A, Sweeney JA, Gong Q (2010). Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by 'resting state' functional magnetic resonance imaging. *Archives of General Psychiatry* **67**, 783–792.

McCormick L, Decker L, Nopoulos P, Ho BC, Andreasen N (2005). Effects of atypical and typical neuroleptics on anterior cingulate volume in schizophrenia. *Schizophrenia Research* **80**, 73–84.

Moncrieff J, Leo J (2010). A systematic review of the effects of antipsychotic drugs on brain volume. *Psychological Medicine* **40**, 1409–1422.

Navari S, Dazzan P (2009). Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychological Medicine* **39**, 1763–1777.

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM (2011). Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biological Psychiatry* **70**, 88–96.

Peters BD, Blaas J, de Haan L (2010). Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? *Journal of Psychiatry Research* **44**, 993–1004.

Peters BD, de Haan L, Dekker N, Blaas J, Becker HE, Dingemans PM, Akkerman EM, Majoie CB, van Amelsvoort T, den Heeten GJ, Linszen DH (2008). White matter fibertracking in first-episode schizophrenia, schizoaffective patients and subjects at ultra-high risk of psychosis. *Neuropsychobiology* **58**, 19–28.

Peters BD, Schmitz N, Dingemans PM, van Amelsvoort TA, Linszen DH, de Haan L, Majoie CB, den Heeten GJ (2009). Preliminary evidence for reduced frontal white matter integrity in subjects at ultra-high-risk for psychosis. *Schizophrenia Research* **111**, 192–193.

Pressler M, Nopoulos P, Ho BC, Andreasen NC (2005). Insular cortex abnormalities in schizophrenia: relationship to symptoms and typical neuroleptic exposure. *Biological Psychiatry* **57**, 394–398.

Rosenberger G, Kubicki M, Nestor PG, Connor E, Bushell GB, Markant D, Niznikiewicz M, Westin CF, Kikinis R, Saykin AJ, McCarley RW, Shenton ME (2008). Age-related deficits in fronto-temporal connections in schizophrenia: a diffusion tensor imaging study. *Schizophrenia Research* **102**, 181–188.

Segal D, Koschnick JR, Slegers LH, Hof PR (2007). Oligodendrocyte pathophysiology: a new view of schizophrenia. *International Journal of Neuropsychopharmacology* **10**, 503–511.

Stephan KE, Baldeweg T, Friston KJ (2006). Synaptic plasticity and dysconnection in schizophrenia. *Biological Psychiatry* **59**, 929–939.

van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RC, Collins DL, Evans AC, Kahn RS (2007). Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. *Neuropsychopharmacology* **32**, 2057–2066.

Vernon AC, Natesan S, Modo M, Kapur S (2011). Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. *Biological Psychiatry* **69**, 936–944.

Wang F, Sun Z, Cui L, Du X, Wang X, Zhang H, Cong Z, Hong N, Zhang D (2004). Anterior cingulum abnormalities in male patients with schizophrenia determined through diffusion tensor imaging. *American Journal of Psychiatry* **161**, 573–575.

Wang Q, Deng W, Huang C, Li M, Ma X, Wang Y, Jiang L, Lui S, Huang X, Chua SE, Cheung C, McAlonan GM, Sham PC, Murray RM, Collier DA, Gong Q, Li T (2011). Abnormalities in connectivity of white-matter tracts in patients with familial and non-familial schizophrenia. *Psychological Medicine* **41**, 1691–1700.

White T, Magnotta VA, Bockholt HJ, Williams S, Wallace S, Ehrlich S, Mueller BA, Ho BC, Jung RE, Clark VP, Lauriello J, Bustillo JR, Schulz SC, Gollub RL, Andreasen NC, Calhoun VD, Lim KO (2011). Global white matter abnormalities in schizophrenia: a multisite diffusion tensor imaging study. *Schizophrenia Bulletin* **37**, 222–232.

https://doi.org/10.1017/S0033291713000238 Published online by Cambridge University Press