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Widespread white-matter microstructure integrity reduction in first-episode schizophrenia patients after acute antipsychotic treatment

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ABSTRACT

Potential effects of initiating acute antipsychotic treatment on white matter (WM) microstructure in schizophrenia patients remain poorly characterized. Thirty-five drug-naïve first-episode schizophrenia patients were scanned before and after six weeks of treatment with second-generation antipsychotic medications. Nineteen demographically matched healthy subjects were scanned twice over the same time interval. Tract-based spatial statistics was used to test for changes in WM microstructural integrity after treatment. Widespread fractional anisotropy (FA) decrease was found in patients after antipsychotic treatment in bilateral posterior corona radiata, anterior corona radiata, superior corona radiata and posterior thalamic radiation, left posterior limb of the internal capsule, and mid-body of the corpus callosum. These effects appeared to result primarily from decreased axial diffusivity. These findings suggest an effect on brain white matter from acute antipsychotic therapy in schizophrenia.

1. Introduction

White matter (WM) abnormalities in schizophrenia have been demonstrated using diffusion tensor imaging (DTI) (Friedman et al. 2008; Fujino et al. 2014; Karbasforoushan et al. 2015; Kubicki and Shenton 2014; Levitt et al. 2017; Roalf et al. 2013; Scheel et al. 2013; Skudlarski et al. 2013; Walther et al. 2011). In most of these studies, patients were receiving antipsychotic treatment. Although never-treated schizophrenia patients have been examined with DTI (Li et al. 2017; Ren et al. 2017), they are not often followed longitudinally to identify treatment-associated WM changes. Antipsychotic medications have been shown to impact gray matter morphometry and brain function both in patients (Ho et al. 2011; Ibi et al. 2017; Jorgensen et al. 2016; Keshavan et al. 1994; Lui et al. 2010) and in animal models (Barr et al. 2013; Song et al. 2017; Vernon et al. 2011). However, whether antipsychotics affect white matter microstructure over the course of treatment remains largely unknown.

Studies of pre- to post-treatment changes in white matter in schizophrenia patients have been limited and yielded inconsistent findings. Reduced (Szeszko et al. 2014; Wang et al. 2013), increased (Ozcelik-Eroglu et al. 2014; Reis Marques et al. 2014) and unaffected (Zeng et al. 2016) integrity of WM over the course of antipsychotic treatment have all been reported. This inconsistency might result from heterogeneity in pre-study antipsychotic exposure, sample differences in illness duration, sometimes small sample sizes, and methodological factors in image analysis (Lener et al. 2015; Tamnes and Agartz 2016).

Although manifestation and mechanism of antipsychotic effects on brain WM microstructure remain unclear in "in vivo" clinical studies, animal and postmortem studies have provided some important insights. After taking antipsychotics at clinic-like plasma levels for 2.5 years, macaque monkeys demonstrated ~10% reduction in both gray and white matter as compared to vehicle (Dorph-Petersen et al. 2005; Konopaske et al. 2007). A follow-up study of the parietal cortex revealed 20% reduction in S100β-immunopositive astrocytes and a non-significant 12.9% reduction in oligodendrocytes (Konopaske et al. 2008), which are the major myelinating cells for axons in central nervous system. Oligodendrocyte density in prefrontal WM has been found to be negatively correlated with lifetime antipsychotic dosage in a postmortem human study (Hercher et al. 2014). While studies of how antipsychotic drugs interact with oligodendrocytes to influence axon myelination represent an active line of current research (Seki et al. 2013; Walterfang et al. 2011; Xu et al. 2011; Zhang et al. 2008), these studies raise the question of whether antipsychotics impact brain white matter in vivo in schizophrenia patients. For instance, a mouse study suggested antipsychotics may facilitate oligodendrocyte development and prevent mice from myelin breakdown (Xiao et al.

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2008). Therefore, clarifying the direction and magnitude of treatment effects on WM in schizophrenia patients is important for clarification of neuropharmacological impact on brain anatomy as well as its potential significance for patients' cognition and general functioning.

The present study performed a longitudinal tract-based spatial statistics (TBSS) (Smith et al. 2006) analysis with first-episode schizophrenia patients. These patients were antipsychotic-naïve before their first MRI scan, and were scanned a second time after six weeks of antipsychotic treatment. Based on preclinical findings, we hypothesized that patients would demonstrate a reduction of WM microstructural integrity after antipsychotic treatment. We also conducted exploratory analyses of the relationship between WM microstructural changes and antipsychotic dosage and symptom improvement after treatment.

2. Materials and methods

2.1. Participants

Thirty-five first-episode schizophrenia patients naïve to psychiatric medications were recruited for this study. Two patients received clopidogrel (25 and 75 mg/d) for protection from a heart attack or stroke. Others did not receive any treatment, and none had received previous antipsychotic therapy. Patients who had to take benzodiazepines for emergency behavioral control were not included in the study. Patients were diagnosed using the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-I/P), and diagnoses were confirmed at one-year follow-up. Illness duration at the time of pretreatment studies was determined as time since patients first met all diagnostic criteria based on interviews with patients and their relatives. Patients were treated with second-generation antipsychotic medications (refer to Table S1 for medication details) according to the treating psychiatrist's preference for six weeks. During the 6-week follow-up, except for the two patients taking clopidogrel, others did not receive any medication other than antipsychotics. Psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) at baseline and follow-up. Dose of antipsychotic medication was converted to chlorpromazine equivalents (Andreasen et al. 2010) for correlational analysis.

Due to the high attrition during follow-up, only nineteen healthy demographically matched volunteers were recruited from the local area. They had been interviewed to ascertain that there was no history of psychiatric illness in first degree relatives and were screened using the SCID Non-Patient Edition to exclude individuals with Axis I disorders. All study participants had no evidence of major medical illness or alcohol/drug abuse, were not pregnant, had no history of neurological disorders or head injury, and were right-handed. The study was approved by the research ethics committee of West China Hospital and all participants provided written informed consent before study participation.

2.2. MRI scans

Participants were scanned with a 3 T MRI scanner (GE SIGNA EXCITE) at both baseline and 6-week follow-up. DTI data were acquired using a single-shot spin-echo echo planar image (SE-EPI) sequence: repetition time/echo time (TR/TE) = 10,000/70.8 ms, matrix = 256 × 256, field of view (FOV) = 24 × 24 cm^2, 42 axial slices, slice thickness = 3 mm, no gap. This sequence led to fifteen diffusion weighted images (b = 1000 s/mm^2) and one image without diffusion gradients (b0). Foam cushions were used to reduce head movement.

2.3. Diffusion MRI data preprocessing

DTI data were preprocessed using the FDT toolbox of FSL (Smith et al. 2004) (http://www.fmrib.ox.ac.uk/fsl). Preprocessing procedures included the following steps: 1) motion and eddy current correction using eddy_correct; 2) skull removal with bet; and 3) tensor model estimation using dtifit to generate three eigenvalue maps (λ_i, i = 1, 2, 3) of the diffusion model and to calculate the fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD) maps.

2.4. TBSS analysis

The well-established TBSS method was applied to test for brain microstructural changes at baseline and after antipsychotic treatment (Smith et al. 2006). FA maps were fed into TBSS pipelines for a series of processing steps including: 1) erosion of maps and zeroing the end slices to remove outliers; 2) registration of FA maps to the FMRIB58_FA template using FNIRT; 3) projection of FA values to the WM fiber skeleton from FSL; and 4) voxel-wise analysis on the skeletonised data using permutation-based non-parametric testing (randomized 5000 times). Permutation used a Student's *t*-test at baseline and a paired *t*-test to test for changes after treatment. Both procedures were implemented using FSL Glm. Threshold-free cluster enhancement (TFCE) was applied to increase sensitivity and identify changes over time in WM measures. Analysis was corrected for multiple comparisons using FWE in comparisons with data distribution from permutations. The significant P-value with the FWE cluster corrected threshold was set at $P < 0.05$ with a cluster size >50 voxels.

Clusters of voxels with significant group differences were localized to anatomical structures using the Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM-DTI-81) WM labels atlas. Mean FA, RD and AD values of voxels within each cluster mask were calculated for each participant.

2.5. Statistical analysis

In addition to testing for change after treatment in the patient group, we conducted a repeated measures ANOVA to test for differential change over time in patients and controls, with age and gender as covariates. For clusters with significant change in the patient group over treatment, Pearson correlations between demographic/clinical variables (dosage of antipsychotic medications in CPZ equivalents, reduction in clinical symptom scores) and FAs of the resultant clusters from TBSS analysis were computed. The statistical results were corrected using false discovery rate (FDR) (Genovese et al. 2002).

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of participants are shown in Table 1. There were no significant differences in age, years of education or gender ratio between patients and healthy controls. Patients exhibited reduced PANSS scores after treatment, with reduced positive symptoms ($P < 0.001$), negative symptoms ($P = 0.001$) and general psychopathological symptoms ($P < 0.001$), and improved global assessment of functioning (GAF) scores ($P < 0.001$).

3.2. WM microstructural integrity at baseline in schizophrenia

At the baseline imaging study, no FA abnormalities were found in first-episode schizophrenia patients compared to healthy controls. There were no RD or AD abnormalities found in patients either.

3.3. FA reduction after acute antipsychotic treatment in schizophrenia

After six weeks of antipsychotic treatment, widespread FA reductions were found in patients relative to their pretreatment scans. These effects were observed in nineteen clusters, including bilateral posterior corona radiata (left, 5 clusters; right, 1 cluster), anterior corona radiata, superior corona radiata (left, 1 cluster; right, 4 clusters), posterior thalamic radiation (including the optic radiation), the left

Table 1
Demographic and clinical information of participants.

–Items	Healthy controls (n = 19)	Patients (n = 35)		t/χ^2	P value
		Baseline	Follow-up		
Age (years)	21.05 ± 5.10	23.83 ± 6.96		1.526	0.133
Education (years)	12.89 ± 2.64	12.46 ± 3.08		0.523	0.603
Gender (female/male)	7:12	19:16		1.501	0.221
Duration of untreated psychosis (months)		7.47 ± 9.88			
PANSS score					
Positive symptoms		27.49 ± 6.21	14.29 ± 4.22	11.182	<0.001
Negative symptoms		18.51 ± 6.55	16.37 ± 6.41	3.515	0.001
General psychopathological symptoms		49.31 ± 8.57	34.23 ± 9.31	10.854	<0.001
GAF score		27.97 ± 8.39	51.86 ± 17.17	7.979	<0.001
Dosage of antipsychotics (mg/d)[a]		–	408.98 ± 150.67		

Abbreviations: PANSS, Positive and Negative Symptom Scale; GAF, Global Assessment of Functioning; s.d., standard deviation. Values are presented in mean ± s.d. format.
[a] Daily dosage of antipsychotic medications in chlorpromazine equivalent.

posterior limb of the internal capsule, right posterior corona radiata emanating from precuneus (2 clusters), and body of the corpus callosum (Fig. 1). Detailed information regarding these clusters of WM showing change after treatment, including MNI coordinates, cluster sizes, effect sizes, and percentage of FA change, is presented in Table 2.

FA values of the nineteen clusters were on average reduced by 4.38 ± 1.60% over the six-week treatment period. As seen in Fig. 2, the FA reduction was almost universal across subjects, and only one out of 35 subjects had an FA increase at the post-treatment scan.

No significant FA changes at follow-up were found using the same procedure in healthy controls. A repeated measures multivariate ANOVA with FAs of these resultant clusters showed significantly greater change in patients than controls over follow-up ($F = 3.073$, $P = 0.002$). Post-hoc repeated measures ANOVAs with FA from each individual cluster indicated that 14 out 19 resultant clusters identified in the pre-post treatment comparison of patients had significant group-by-time interaction effects, indicating changes in patients that were significantly greater than controls over the follow-up period (Table S2).

3.4. AD reduction

Among regions with significant FA reduction, significant AD reduction was found for two clusters in the left posterior corona radiata ($t = 3.205$, corrected $P = 0.014$; $t = 3.775$, corrected $P = 0.006$), one cluster in right posterior thalamic radiation including the optic radiation ($t = 3.621$, corrected $P = 0.006$), one cluster in right posterior corona radiata ($t = 3.932$, corrected $P = 0.006$), and one cluster in right superior corona radiate ($t = 3.094$, corrected $P = 0.015$). No region showed a significant increase in AD or significant change in RD.

3.5. Association between demographic/clinical factors and FA changes

Fig. 3 depicts the association between demographic/clinical factors and FA changes. Dosage of antipsychotic medications was positively correlated with FA changes in two clusters of the right superior corona radiata ($r = 0.462$, $P = 0.020$; $r = 0.505$, $P = 0.010$; uncorrected). No significant correlation was found between FA changes and changes in

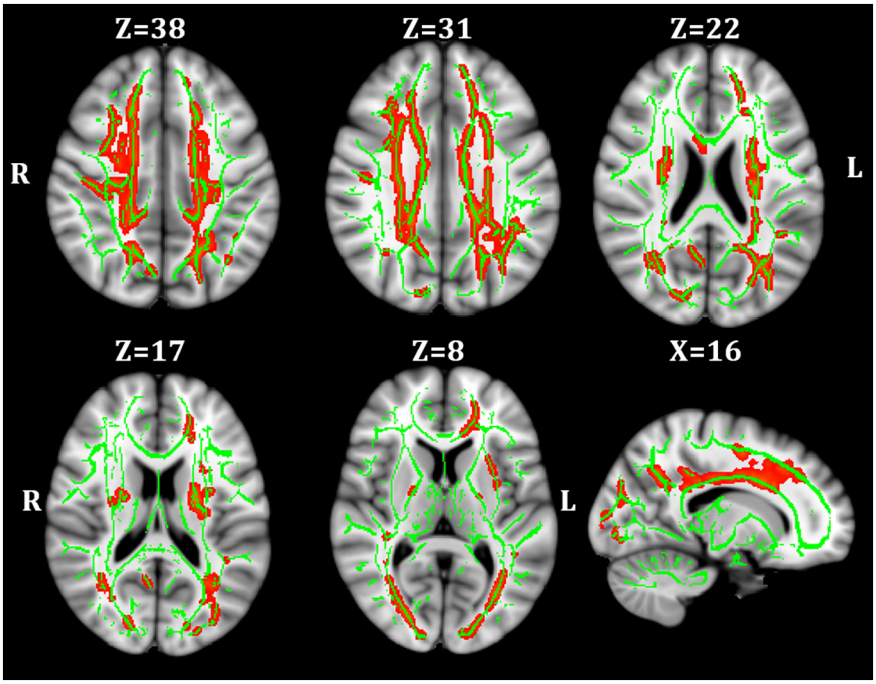

Fig. 1. Widespread FA reduction in schizophrenia patients after acute antipsychotic treatment. Regions with significant FA decrease are highlighted in red/orange. The image in gray is the MNI152 template. Skeletons of major fiber tracts are highlighted in green and overlaid onto the template. Abbreviations: L, left; R, right.

Table 2
Regions showing significant change of DTI parameters in schizophrenia patients after treatment.

Brain regions	Cluster size	MNI coordinate (X, Y, Z)	T value	Cohen's d	FA decrease (%)
Fractional anisotropy (Baseline > Follow-up)					
[a]Posterior corona radiata L	252	−25, −27, 34	5.16	0.87	5.19
	111	−27, −61, 22	4.4	0.74	3.75
	103	−20, −60, 34	3.74	0.63	3.74
	77	−19, −36, 36	3.85	0.65	3.38
	61	−19, -26, 50	3.29	0.56	4.40
Anterior corona radiata L	74	−19, 24, 36	4.73	0.79	4.03
Superior corona radiata L	55	−29, −16, 24	4.02	0.68	2.65
Posterior limb of internal capsule L	76	−21, −8, 14	3.91	0.66	3.42
Posterior thalamic radiation (include optic radiation) L	71	−34, −61, 12	3.97	0.67	2.87
[a]Posterior thalamic radiation (include optic radiation) R	154	25, −79, 7	4.02	0.68	3.75
Anterior corona radiata R	96	21, 25, 34	3.81	0.64	4.53
[a]Posterior corona radiata R	75	25, −30, 33	3.85	0.65	3.79
[a]Superior corona radiata R	244	26, −11, 33	5.3	0.89	4.63
	98	25, −23, 31	3.38	0.57	3.20
	88	27, 1, 43	3.98	0.67	5.93
	65	16, 4, 34	3.05	0.52	3.47
Posterior corona radiata extending to precuneus R	73	7, −60, 21	3.74	0.63	7.37
	75	13, −74, 41	3.64	0.62	9.17
Body of corpus callosum	96	16, 12, 31	4.35	0.74	3.95

[a] Regions showing significant difference in AD over the follow-up ($P < 0.05$, FDR corrected).

ratings of psychiatric symptom severity, years of education, or duration of illness.

4. Discussion

The present study observed widespread FA reductions in white matter in previously untreated first-episode schizophrenia patients after 6 weeks of antipsychotic treatment. No significant brain microstructure changes were detected before treatment. The FA reductions in the right superior corona radiata were correlated with the dosage of antipsychotic medications. Since reductions in WM integrity occurred after acute treatment during which marked clinical recovery was observed in patients who had been typically experiencing psychotic symptoms for several months prior to treatment, the possibility of dramatic illness progression effects causing our 6-week follow-up study seems unlikely. Rather, in the context of occurring during clinical recovery, the findings may most likely represent the effects of acute antipsychotic treatment on WM brain microstructural integrity in schizophrenia patients.

There was an apparently anti-intuitive dissociation of adverse WM changes in the context of clinical improvement in psychological functioning. However, in medicine, there are many instances in which improving target symptoms but causing adverse effects, such as hormone and nonsteroidal anti-inflammatory drugs (Ho et al. 2011). Most antipsychotics have an increased risk of causing weight gain and disturbances in glucose and lipid metabolism (Miyamoto et al. 2012). It is possible that, although antipsychotics relieve psychosis and its attendant suffering, they cannot arrest or reverse an injurious process occurring in the brain of patients related to schizophrenia biology, or that

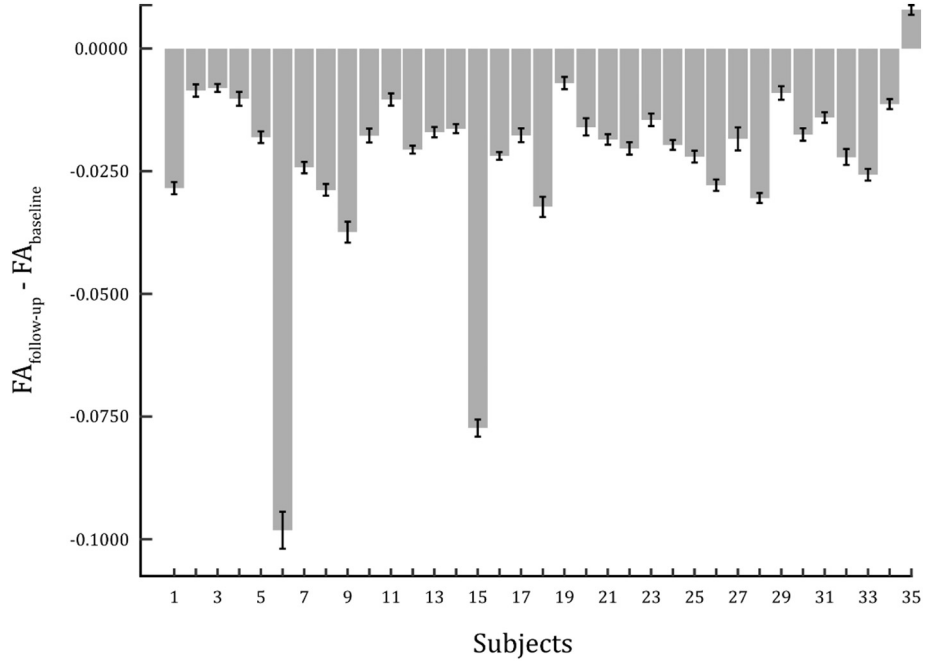

Fig. 2. Average FA changes across nineteen regions with significant FA decrease over 6 weeks in each individual patient. Axis-x stands for the index of individual schizophrenia patients and axis-y stands for changes of FA over the treatment. The FA changes were averaged across the nineteen ROIs in Table 2.

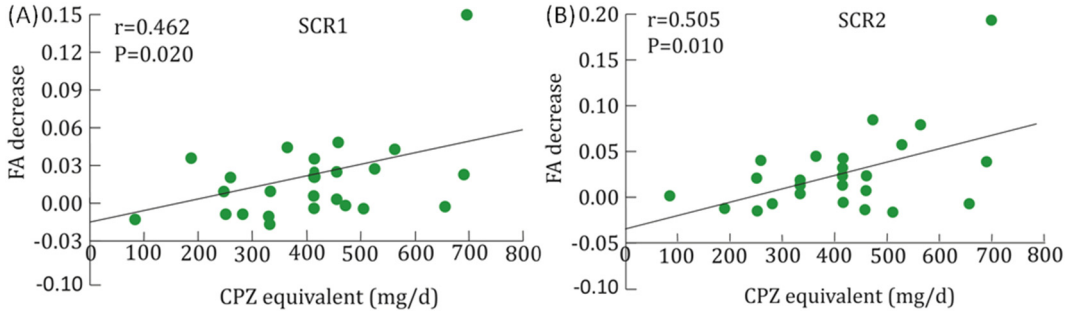

Fig. 3. Positive correlations between antipsychotic dosages and FA decreases in clusters of the right SCR. Abbreviations: SCR, superior corona radiata; CPZ, chlorpromazine. FA decrease = $FA_{baseline} - FA_{follow-up}$.

they may directly worsen or cause WM pathology (Ho et al. 2011; Wang et al. 2013). There were also other studies showing similar dissociations, including reduction in frontal connectivity (Lui et al. 2010), reductions in dorsolateral prefrontal cortex (DLPFC) activation during task-based neurocognitive studies (Keedy et al. 2014), reduced performance on a procedural learning test (Harris et al. 2009), relations of antipsychotic dosage to poorer performance on neuropsychological tests of prefrontal function (Sweeney et al. 1991), and studies of working memory using identical paradigms as used in nonhuman primates to show adverse effects of short term antipsychotic treatment (Reilly et al. 2007) - the severity of which was predicted by glutamate-related genetic traits (Bishop et al. 2015). All of these effects were seen in the context of reductions in psychosis severity that is well established benefit of antipsychotic treatment especially in the early course illness.

Considering the significant integrity of WM reduction after treatment, the interpretation is consistent with several prior studies that have shown similar effects of antipsychotic medications on brain WM. Initial studies in this area showed that antipsychotic treatment was linked to reduced WM volume (Girgis et al. 2006; Ho et al. 2011; Molina et al. 2005). In more recent studies of WM microstructure with DTI, integrity reduction was found after antipsychotic treatment in a whole-brain voxel-wise manner (Szeszko et al. 2014; Wang et al. 2013). Our study advanced this line of research by integrating fiber skeleton priors into the analysis. By projecting FA values of nearby WM tissue onto fiber skeletons rather than smoothing homogenously within a certain kernel, the applied longitudinal TBSS method alleviated partial volume effects and improved statistical sensitivity. Moreover, our study with drug-naïve schizophrenia patients excluded the potential confounding effect of prior antipsychotic exposure.

Our study did not demonstrate abnormalities in the WM of untreated patients with first episode schizophrenia in contrast with previous findings in treated patients with first episode schizophrenia (Lee et al. 2013; Ruef et al. 2012), and in untreated patients with chronic schizophrenia (Liu et al. 2013), using the same technique as we did. The contrasting findings of these studies suggest that in the early stages of schizophrenia, WM integrity is normal or that pathological changes are too subtle to be detected with this technique, and that neuropathological changes in WM may be a result of antipsychotic medications or a progressive and chronic illness, at least in some patients. Several studies have also reported negative results in first-episode schizophrenia (Friedman et al. 2008; Kong et al. 2011; Konrad and Winterer 2007; White et al. 2009), however, using TBSS technique, there is considerable variability among WM investigations in untreated first episode patients (Guo et al. 2012; Alvarado-Alanis et al. 2015). Several likely factors may contribute to this heterogeneity, such as the heterogeneity of clinical presentation in schizophrenia, moderator variables across studies (age of onset, gender, and parental socio-economic status) (Sun et al. 2015; Wheeler and Voineskos 2014).

We found widespread FA reduction in patients, which differs from the pattern of specific focal FA reduction reported in previous studies (Szeszko et al. 2014; Wang et al. 2013). The difference may result from the more sensitive analysis procedure and limited confounding factors in our study. Diffuse rather than specific FA reduction might contribute to various adverse effects of antipsychotic medications on brain, including dosage related changes in neuropsychological functioning (Sweeney et al. 1991), perturbation of saccadic eye movements (Sweeney et al. 1997) and changes in specific cognitive abilities seen in neurophysiological and fMRI studies (Keedy et al. 2009; Reilly et al. 2006). Moreover, the FA reductions in the right superior corona radiata were correlated with the dosage of antipsychotic medications. Superior corona radiata locates in frontal and parietal lobes. It is possible that those brain regions are more sensitive to antipsychotics, which have been reported in previous studies (Dorph-Petersen et al. 2005; Miller et al. 2001; Molina et al. 2005; Moncrieff and Leo 2010).

How antipsychotic drugs might affect WM microstructural integrity remains unclear. Second-generation antipsychotics are believed to increase serum cholesterol and disrupt lipid metabolism, elevating risks of cardiometabolic disease (Bushe and Paton 2005; De Hert et al. 2011; Hoffmann et al. 2010). Increased serum lipid levels including high low-density lipoprotein (LDL) has been associated with lower WM integrity in healthy individuals (Williams et al. 2013). Similarly, for first-episode psychosis patients, FA reductions have been associated with increased LDL after 12-week of antipsychotic treatment (Szeszko et al. 2014). Whether and how increased serum cholesterol and other drug effects may relate to decreased WM microstructure integrity are questions for further study.

Our longitudinal analysis revealed decreased FA in WM structures, accompanied with decreased AD value rather than increased RD. This suggests that the decreased microstructure integrity may be primarily a result of axonal degeneration (Song et al. 2003). However, previous study found FA reductions with AD decreases and RD increases following 12 weeks of antipsychotic treatment, which supports the possibility that axonal and myelin-related properties of the white matter may be altered simultaneously (Szeszko et al. 2014). In pathological conditions of the nervous system, axonal damage, myelin loss, and reactive processes tend to occur in unison (Dwork et al. 2007). Considering longer medication exposure of Szeszko et al. study than that of our study, we deduced that myelin loss may be subtle at early phase of antipsychotic treatment, and obvious gradually. A decreased number of glial cells including oligodendrocytes which form the myelin sheath after chronic antipsychotic treatment has been reported in an animal study (Konopaske et al. 2008). Parallel animal studies are necessary to confirm this hypothesis and better determine the time course of antipsychotics effects on WM.

Several issues should be considered when interpreting our results. First, disease progression might still contribute to changes in WM microstructure integrity, although the time interval over the follow-up was short and the illness effects were not significant at the baseline. In addition, other potential effects associated with white matter alterations over time include smoking (Gons et al. 2011), body mass index (Verstynen et al. 2012), and extracellular water alterations in WM (Oestreich et al. 2017; Pasternak et al. 2012). Second, the sample size

of the study is not large, and replication in a larger sample is needed to confirm study findings and to establish whether these effects are seen in a subgroup of patients or are more universally observed. Third, extensive studies of cognition, measurements of serum lipid metabolism and other clinical features are not available for this patient sample. Forth, dosage of antipsychotic medications was not significantly correlated with FA reduction in right superior corona radiata after FDR correction. Finally, the limited gradient directions in the present study kept us from using sophisticated diffusion models.

5. Conclusions

The present study suggests that at the early phase of schizophrenia, short-term antipsychotic treatment may lead to widespread reduction in WM microstructure integrity, and therefore adds to the development of psychoradiology (https://radiopaedia.org/articles/psychoradiology) (Kressel 2017; Lui et al. 2016; Port 2018; Sun et al. 2018). Studies on the underlying mechanism and effects of long-term antipsychotic treatment on brain microstructure are warranted in the future.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.08.021.

References

Alvarado-Alanis, P., León-Ortiz, P., Reyes-Madrigal, F., Favila, R., Rodríguez-Mayoral, O., Nicolini, H., Azcárraga, M., Graff-Guerrero, A., Rowland, L.M., de la Fuente-Sandoval, C., 2015. Abnormal white matter integrity in antipsychotic-naïve first-episode psychosis patients assessed by a DTI principal component analysis. Schizophr. Res. 162, 14–21.

Andreasen, N.C., Pressler, M., Nopoulos, P., Miller, D., Ho, B.C., 2010. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol. Psychiatry 67, 255–262.

Barr, A.M., Wu, C.H., Wong, C., Hercher, C., Topfer, E., Boyda, H.N., Procyshyn, R.M., Honer, W.G., Beasley, C.L., 2013. Effects of chronic exercise and treatment with the antipsychotic drug olanzapine on hippocampal volume in adult female rats. Neuroscience 255, 147–157.

Bishop, J.R., Reilly, J.L., Harris, M.S., Patel, S.R., Kittles, R., Badner, J.A., Prasad, K.M., Nimgaonkar, V.L., Keshavan, M.S., Sweeney, J.A., 2015. Pharmacogenetic associations of the type-3 metabotropic glutamate receptor (GRM3) gene with working memory and clinical symptom response to antipsychotics in first-episode schizophrenia. Psychopharmacology 232, 145–154.

Bushe, C., Paton, C., 2005. The potential impact of antipsychotics on lipids in schizophrenia: is there enough evidence to confirm a link? J. Psychopharmacol. 19, 76–83.

De Hert, M., Detraux, J., van Winkel, R., Yu, W., Correll, C.U., 2011. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat. Rev. Endocrinol. 8, 114–126.

Dorph-Petersen, K.A., Pierri, J.N., Perel, J.M., Sun, Z., Sampson, A.R., Lewis, D.A., 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.

Dwork, A.J., Mancevski, B., Rosoklija, G., 2007. White matter and cognitive function in schizophrenia. Int. J. Neuropsychopharmacol. 10, 513–536.

Friedman, J.I., Tang, C., Carpenter, D., Buchsbaum, M., Schmeidler, J., Flanagan, L., Golembo, S., Kanellopoulou, I., Ng, J., Hof, P.R., Harvey, P.D., Tsopelas, N.D., Stewart, D., Davis, K.L., 2008. Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. Am. J. Psychiatry 165, 1024–1032.

Fujino, J., Takahashi, H., Miyata, J., Sugihara, G., Kubota, M., Sasamoto, A., Fujiwara, H., Aso, T., Fukuyama, H., Murai, T., 2014. Impaired empathic abilities and reduced white matter integrity in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 48, 117–123.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15, 870–878.

Girgis, R.R., Diwadkar, V.A., Nutche, J.J., Sweeney, J.A., Keshavan, M.S., Hardan, A.Y., 2006. Risperidone in first-episode psychosis: a longitudinal, exploratory voxel-based morphometric study. Schizophr. Res. 82, 89–94.

Gons, R.A., van Norden, A.G., de Laat, K.F., van Oudheusden, L.J., van Uden, I.W., Zwiers, M.P., Norris, D.G., de Leeuw, F.-E., 2011. Cigarette smoking is associated with reduced microstructural integrity of cerebral white matter. Brain 134, 2116–2124.

Guo, W., Liu, F., Liu, Z., Gao, K., Xiao, C., Chen, H., Zhao, J., 2012. Right lateralized white matter abnormalities in first-episode, drug-naive paranoid schizophrenia. Neurosci. Lett. 531, 5–9.

Harris, M.S., Wiseman, C.L., Reilly, J.L., Keshavan, M.S., Sweeney, J.A., 2009. Effects of risperidone on procedural learning in antipsychotic-naive first-episode schizophrenia. Neuropsychopharmacology 34, 468.

Hercher, C., Chopra, V., Beasley, C.L., 2014. Evidence for morphological alterations in prefrontal white matter glia in schizophrenia and bipolar disorder. J. Psychiatry Neurosci. 39, 376–385.

Ho, B.C., Andreasen, N.C., Ziebell, S., Pierson, R., Magnotta, V., 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch. Gen. Psychiatry 68, 128–137.

Hoffmann, V.P., Case, M., Stauffer, V.L., Jacobson, J.G., Conley, R.R., 2010. Predictive value of early changes in triglycerides and weight for longer-term changes in metabolic measures during olanzapine, ziprasidone or aripiprazole treatment for schizophrenia and schizoaffective disorder post hoc analyses of 3 randomized, controlled clinical trials. J. Clin. Psychopharmacol. 30, 656–660.

Ibi, D., de la Fuente Revenga, M., Kezunovic, N., Muguruza, C., Saunders, J.M., Gaitonde, S.A., Moreno, J.L., Ijaz, M.K., Santosh, V., Kozlenkov, A., Holloway, T., Seto, J., Garcia-Bea, A., Kurita, M., Mosley, G.E., Jiang, Y., Christoffel, D.J., Callado, L.F., Russo, S.J., Dracheva, S., Lopez-Gimenez, J.F., Ge, Y., Escalante, C.R., Meana, J.J., Akbarian, S., Huntley, G.W., Gonzalez-Maeso, J., 2017. Antipsychotic-induced Hdac2 transcription via NF-kappaB leads to synaptic and cognitive side effects. Nat. Neurosci. 20, 1247–1259.

Jorgensen, K.N., Nesvag, R., Gunleiksrud, S., Raballo, A., Jonsson, E.G., Agartz, I., 2016. First- and second-generation antipsychotic drug treatment and subcortical brain morphology in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 266, 451–460.

Karbasforoushan, H., Duffy, B., Blackford, J.U., Woodward, N.D., 2015. Processing speed impairment in schizophrenia is mediated by white matter integrity. Psychol. Med. 45, 109–120.

Keedy, S.K., Rosen, C., Khine, T., Rajarethinam, R., Janicak, P.G., Sweeney, J.A., 2009. An fMRI study of visual attention and sensorimotor function before and after antipsychotic treatment in first-episode schizophrenia. Psychiatry Res. 172, 16–23.

Keedy, S.K., Reilly, J.L., Bishop, J.R., Weiden, P.J., Sweeney, J.A., 2014. Impact of antipsychotic treatment on attention and motor learning systems in first-episode schizophrenia. Schizophr. Bull. 41, 355–365.

Keshavan, M.S., Bagwell, W.W., Haas, G.L., Sweeney, J.A., Schooler, N.R., Pettegrew, J.W., 1994. Changes in caudate volume with neuroleptic treatment. Lancet 344, 1434.

Kong, X., Ouyang, X., Tao, H., Liu, H., Li, L., Zhao, J., Xue, Z., Wang, F., Jiang, S., Shan, B., 2011. Complementary diffusion tensor imaging study of the corpus callosum in patients with first-episode and chronic schizophrenia. J. Psychiatry Neurosci. 36, 120.

Konopaske, G.T., Dorph-Petersen, K.A., Pierri, J.N., Wu, Q., Sampson, A.R., Lewis, D.A., 2007. Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. Neuropsychopharmacology 32, 1216–1223.

Konopaske, G.T., Dorph-Petersen, K.A., Sweet, R.A., Pierri, J.N., Zhang, W., Sampson, A.R., Lewis, D.A., 2008. Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. Biol. Psychiatry 63, 759–765.

Konrad, A., Winterer, G., 2007. Disturbed structural connectivity in schizophrenia—primary factor in pathology or epiphenomenon? Schizophr. Bull. 34, 72–92.

Kressel, H.Y., 2017. Setting sail: 2017. Radiology 282, 4–6.

Kubicki, M., Shenton, M.E., 2014. Diffusion tensor imaging findings and their implications in schizophrenia. Curr. Opin. Psychiatry 27, 179–184.

Lee, S.-H., Kubicki, M., Asami, T., Seidman, L.J., Goldstein, J.M., Mesholam-Gately, R.I., McCarley, R.W., Shenton, M.E., 2013. Extensive white matter abnormalities in patients with first-episode schizophrenia: a diffusion tensor imaging (DTI) study. Schizophr. Res. 143, 231–238.

Lener, M.S., Wong, E., Tang, C.Y., Byne, W., Goldstein, K.E., Blair, N.J., Haznedar, M.M., New, A.S., Chemerinski, E., Chu, K.W., Rimsky, L.S., Siever, L.J., Koenigsberg, H.W., Hazlett, E.A., 2015. White matter abnormalities in schizophrenia and schizotypal personality disorder. Schizophr. Bull. 41, 300–310.

Levitt, J.J., Nestor, P.G., Levin, L., Pelavin, P., Lin, P., Kubicki, M., McCarley, R.W., Shenton, M.E., Rathi, Y., 2017. Reduced structural connectivity in frontostriatal white matter tracts in the associative loop in schizophrenia. Am. J. Psychiatry 174, 1102–1111.

Li, F., Lui, S., Yao, L., Ji, G.J., Liao, W., Sweeney, J.A., Gong, Q., 2017. Altered white matter connectivity within and between networks in antipsychotic-naive first-episode schizophrenia. Schizophr. Bull. 44, 409–418.

Liu, X., Lai, Y., Wang, X., Hao, C., Chen, L., Zhou, Z., Yu, X., Hong, N., 2013. Reduced white matter integrity and cognitive deficit in never-medicated chronic schizophrenia: a diffusion tensor study using TBSS. Behav. Brain Res. 252, 157–163.

Lui, S., Li, T., Deng, W., Jiang, L., Wu, Q., Tang, H., Yue, Q., Huang, X., Chan, R.C., Collier, D.A., Meda, S.A., Pearlson, G., Mechelli, A., Sweeney, J.A., 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. Arch. Gen. Psychiatry 67, 783–792.

Lui, S., Zhou, X.J., Sweeney, J.A., Gong, Q., 2016. Psychoradiology: the frontier of neuroimaging in psychiatry. Radiology 281, 357–372.

Miller, D.D., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Boles Ponto, L.L., Hichwa, R.D., 2001. Comparison of the effects of risperidone and haloperidol on regional cerebral blood flow in schizophrenia. Biol. Psychiatry 49, 704–715.

Miyamoto, S., Miyake, N., Jarskog, L., Fleischhacker, W., Lieberman, J., 2012. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol. Psychiatry 17, 1206.
Molina, V., Reig, S., Sanz, J., Palomo, T., Benito, C., Sanchez, J., Sarramea, F., Pascau, J., Desco, M., 2005. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. Schizophr. Res. 80, 61–71.
Moncrieff, J., Leo, J., 2010. A systematic review of the effects of antipsychotic drugs on brain volume. Psychol. Med. 40, 1409–1422.
Oestreich, L.K., Lyall, A.E., Pasternak, O., Kikinis, Z., Newell, D.T., Savadjiev, P., Bouix, S., Shenton, M.E., Kubicki, M., Whitford, T.J., 2017. Characterizing white matter changes in chronic schizophrenia: a free-water imaging multi-site study. Schizophr. Res. 189, 153–161.
Ozcelik-Eroglu, E., Ertugrul, A., Oguz, K.K., Has, A.C., Karahan, S., Yazici, M.K., 2014. Effect of clozapine on white matter integrity in patients with schizophrenia: a diffusion tensor imaging study. Psychiatry Res. 223, 226–235.
Pasternak, O., Westin, C.-F., Bouix, S., Seidman, L.J., Goldstein, J.M., Woo, T.-U.W., Petryshen, T.L., Mesholam-Gately, R.I., McCarley, R.W., Kikinis, R., 2012. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. J. Neurosci. 32, 17365–17372.
Port, J.D., 2018. Diagnosis of attention deficit hyperactivity disorder by using MR imaging and radiomics: a potential tool for clinicians. Radiology 287, 631–632.
Reilly, J.L., Harris, M.S., Keshavan, M.S., Sweeney, J.A., 2006. Adverse effects of risperidone on spatial working memory in first-episode schizophrenia. Arch. Gen. Psychiatry 63, 1189–1197.
Reilly, J.L., Harris, M.S., Khine, T.T., Keshavan, M.S., Sweeney, J.A., 2007. Antipsychotic drugs exacerbate impairment on a working memory task in first-episode schizophrenia. Biol. Psychiatry 62, 818–821.
Reis Marques, T., Taylor, H., Chaddock, C., Dell'acqua, F., Handley, R., Reinders, A.A., Mondelli, V., Bonaccorso, S., Diforti, M., Simmons, A., David, A.S., Murray, R.M., Pariante, C.M., Kapur, S., Dazzan, P., 2014. White matter integrity as a predictor of response to treatment in first episode psychosis. Brain 137, 172–182.
Ren, H.Y., Wang, Q., Lei, W., Zhang, C.C., Li, Y.F., Li, X.J., Li, M.L., Deng, W., Huang, C.H., Du, F., Zhao, L.S., Wang, Y.C., Ma, X.H., Hu, X., Li, T., 2017. The common variants implicated in microstructural abnormality of first episode and drug-naive patients with schizophrenia. Sci. Rep. 7, 11750.
Roalf, D.R., Ruparel, K., Verma, R., Elliott, M.A., Gur, R.E., Gur, R.C., 2013. White matter organization and neurocognitive performance variability in schizophrenia. Schizophr. Res. 143, 172–178.
Ruef, A., Curtis, L., Moy, G., Bessero, S., Bâ, M.B., Lazeyras, F., Lövblad, K.-O., Haller, S., Malafosse, A., Giannakopoulos, P., 2012. Magnetic resonance imaging correlates of first-episode psychosis in young adult male patients: combined analysis of grey and white matter. J. Psychiatry Neurosci. 37, 305.
Scheel, M., Prokscha, T., Bayerl, M., Gallinat, J., Montag, C., 2013. Myelination deficits in schizophrenia: evidence from diffusion tensor imaging. Brain Struct. Funct. 218, 151–156.
Seki, Y., Kato, T.A., Monji, A., Mizoguchi, Y., Horikawa, H., Sato-Kasai, M., Yoshiga, D., Kanba, S., 2013. Pretreatment of aripiprazole and minocycline, but not haloperidol, suppresses oligodendrocyte damage from interferon-gamma-stimulated microglia in co-culture model. Schizophr. Res. 151, 20–28.
Skudlarski, P., Schretlen, D.J., Thaker, G.K., Stevens, M.C., Keshavan, M.S., Sweeney, J.A., Tamminga, C.A., Clementz, B.A., O'Neil, K., Pearlson, G.D., 2013. Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. Am. J. Psychiatry 170, 886–898.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23 (Suppl. 1), S208–S219.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 31, 1487–1505.
Song, S.K., Sun, S.W., Ju, W.K., Lin, S.J., Cross, A.H., Neufeld, A.H., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. NeuroImage 20, 1714–1722.
Song, W.S., Cha, J.H., Yoon, S.H., Cho, Y.S., Park, K.Y., Kim, M.H., 2017. The atypical antipsychotic olanzapine disturbs depotentiation by modulating mAChRs and impairs reversal learning. Neuropharmacology 114, 1–11.
Sun, H., Lui, S., Yao, L., Deng, W., Xiao, Y., Zhang, W., Huang, X., Hu, J., Bi, F., Li, T., Sweeney, J.A., Gong, Q., 2015. Two patterns of white matter abnormalities in medication-naive patients with first-episode schizophrenia revealed by diffusion tensor imaging and cluster analysis. JAMA Psychiatry 72, 678–686.
Sun, H., Chen, Y., Huang, Q., Liu, S., Huang, X., Shi, Y., Xu, X., Sweeney, J.A., Gong, Q., 2018. Psychoradiologic utility of MR imaging for diagnosis of attention deficit hyperactivity disorder: a radiomics analysis. Radiology 287, 620–630.
Sweeney, J.A., Keilp, J.G., Haas, G.L., Hill, J., Weiden, P.J., 1991. Relationships between medication treatments and neuropsychological test performance in schizophrenia. Psychiatry Res. 37, 297–308.
Sweeney, J.A., Bauer, K.S., Keshavan, M.S., Haas, G.L., Schooler, N.R., Kroboth, P.D., 1997. Adverse effects of risperidone on eye movement activity: a comparison of risperidone and haloperidol in antipsychotic-naive schizophrenic patients. Neuropsychopharmacology 16, 217–228.
Szeszko, P.R., Robinson, D.G., Ikuta, T., Peters, B.D., Gallego, J.A., Kane, J., Malhotra, A.K., 2014. White matter changes associated with antipsychotic treatment in first-episode psychosis. Neuropsychopharmacology 39, 1324–1331.
Tamnes, C.K., Agartz, I., 2016. White matter microstructure in early-onset schizophrenia: a systematic review of diffusion tensor imaging studies. J. Am. Acad. Child Adolesc. Psychiatry 55, 269–279.
Vernon, A.C., 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. Biol. Psychiatry 69, 936–944.
Verstynen, T.D., Weinstein, A.M., Schneider, W.W., Jakicic, J.M., Rofey, D.L., Erickson, K.I., 2012. Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. Psychosom. Med. 74, 682.
Walterfang, M., Velakoulis, D., Whitford, T.J., Pantelis, C., 2011. Understanding aberrant white matter development in schizophrenia: an avenue for therapy? Expert. Rev. Neurother. 11, 971–987.
Walther, S., Federspiel, A., Horn, H., Razavi, N., Wiest, R., Dierks, T., Strik, W., Muller, T.J., 2011. Alterations of white matter integrity related to motor activity in schizophrenia. Neurobiol. Dis. 42, 276–283.
Wang, Q., Cheung, C., Deng, W., Li, M., Huang, C., Ma, X., Wang, Y., Jiang, L., Sham, P.C., Collier, D.A., Gong, Q., Chua, S.E., McAlonan, G.M., Li, T., 2013. White-matter microstructure in previously drug-naive patients with schizophrenia after 6 weeks of treatment. Psychol. Med. 43, 2301–2309.
Wheeler, A.L., Voineskos, A.N., 2014. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. Front. Hum. Neurosci. 8, 653.
White, T., Magnotta, V.A., Bockholt, H.J., Williams, S., Wallace, S., Ehrlich, S., Mueller, B.A., Ho, B.-C., Jung, R.E., Clark, V.P., 2009. Global white matter abnormalities in schizophrenia: a multisite diffusion tensor imaging study. Schizophr. Bull. 37, 222–232.
Williams, V.J., Leritz, E.C., Shepel, J., McGlinchey, R.E., Milberg, W.P., Rudolph, J.L., Lipsitz, L.A., Salat, D.H., 2013. Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. Hum. Brain Mapp. 34, 1826–1841.
Xiao, L., Xu, H., Zhang, Y., Wei, Z., He, J., Jiang, W., Li, X., Dyck, L.E., Devon, R.M., Deng, Y., Li, X.M., 2008. Quetiapine facilitates oligodendrocyte development and prevents mice from myelin breakdown and behavioral changes. Mol. Psychiatry 13, 697–708.
Xu, H., Yang, H.J., Rose, G.M., Li, X.M., 2011. Recovery of behavioral changes and compromised white matter in C57BL/6 mice exposed to cuprizone: effects of antipsychotic drugs. Front. Behav. Neurosci. 5, 31.
Zeng, B., Ardekani, B.A., Tang, Y., Zhang, T., Zhao, S., Cui, H., Fan, X., Zhuo, K., Li, C., Xu, Y., Goff, D.C., Wang, J., 2016. Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. Schizophr. Res. 172, 1–8.
Zhang, Y., Xu, H., Jiang, W., Xiao, L., Yan, B., He, J., Wang, Y., Bi, X., Li, X., Kong, J., Li, X.M., 2008. Quetiapine alleviates the cuprizone-induced white matter pathology in the brain of C57BL/6 mouse. Schizophr. Res. 106, 182–191.