Schizophrenia Research 109 (2009) 167–181

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

White matter abnormalities in schizophrenia patients with tardive dyskinesia: A diffusion tensor image study

Ya Mei Bai [a,b], Kun-Hsien Chou [c], Ching-Po Lin [d,e,f,*,1], I-Yun Chen [d], Cheng-Ta Li [a], Kai Chun Yang [a], Yuan-Hwa Chou [a,b], Tung-Ping Su [a,b,d,f,*,1]

[a] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Psychiatry, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[d] Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan
[e] MRI research center, National Yang-Ming University, Taipei, Taiwan
[f] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 16 December 2008
Received in revised form 5 February 2009
Accepted 5 February 2009
Available online 3 March 2009

Keywords:
White matter
Schizophrenia
Tardive dyskinesia

ABSTRACT

Objective: Tardive dyskinesia (TD) is a severe side effect of antipsychotics. While increasing evidence suggests that damaged brain microcircuitry of white matter (WM) is responsible for the clinical symptoms in schizophrenia, no reports of WM abnormality associated with TD were noted.

Method: Brain white matter abnormalities were investigated among 20 schizophrenia patients with TD (Schizophrenia with TD group), 20 age-, gender-, and handedness-matched schizophrenic patients without TD (Schizophrenia without TD group), and 20 matched healthy subjects with magnetic resonance imaging and diffusion tensor imaging analysis. Voxel-wise analysis was used to compare fractional anisotropy (FA) maps of the white matter following intersubject registration to Talairach space. Clinical ratings included the Positive and Negative Symptoms Scale (PANSS), Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS).

Results: The study subjects were 75% female with average of 40.1 ± 9.8 years. The Schizophrenia with TD group had significantly higher PANSS total scores ($p = 0.024$), PANSS negative score ($p = 0.001$), SAS ($p < 0.001$) and AIMS ($p < 0.001$) scores; and demonstrated more widespread FA decreases than the Schizophrenia without TD group, especially over the inferior frontal gyrus, temporal sublobar extranuclear WM (around the basal ganglion), parietal precuneus gyrus WM (around somatosensory cortex), and medial frontal gyrus WM (around dorsolateral prefrontal cortex). The AIMS ($p < 0.01$) and SAS ($p < 0.01$) score positively correlated with decreased FA over these areas, and PANSS negative score positively correlated with FA decrease over medial frontal gyrus WM ($p < 0.01$).

Conclusions: More widespread abnormality of white matter was noted among schizophrenia patients than those without, especially involved cortico-basal ganglion circuits with clinical symptom correlation of involuntary movements and negative symptoms. Further studies with larger sample size are required to validate the findings.

* Corresponding authors. Su is to be contacted at No. 201, Sec. 2, Shih-Pai Road, Taipei 112, Taiwan. Tel.: +886 2 28757027; fax: +886 2 28757592. Lin, 155 Li-Nong St., Sec. 2, Peitou, Taipei, Taiwan. Tel.: +886 2 28267338; fax: +886 2 28262285.
E-mail addresses: cplin@ntu.edu.tw (C.-P. Lin), tpsu@vghtpe.gov.tw (T.-P. Su).
[1] Dr. Su for the clinical part, and Dr. Lin for the Image part.

0920-9964/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2009.02.003

1. Introduction

Tardive dyskinesia (TD), a severe and disabling side effect of antipsychotics, is characterized by late-onset, repetitive, involuntary choreiform movements, tics and grimaces of the orofacial muscles, and dyskinesia of the distal limbs, paraspinal muscles, and diaphragm (Miller et al., 2005). Schizophrenic patients with TD have an unusually high incidence of cognitive impairment and negative symptoms (Berry et al., 2007). These symptoms frequently continue and may become permanent even after antipsychotics are discontinued (Bai et al., 2003). A recent report showed that the annualized incidence of TD was 5.5% with first-generation antipsychotics, and 3.9% with second-generation antipsychotics (Correll and Schenk, 2008). This incidence of TD with atypical antipsychotics was higher than expected, and underscores the fact that TD is still a significant clinical problem (Chouinard, 2006).

It has been hypothesized that schizophrenic patients with TD have more neurodevelopmental disturbances, particularly minor physical anomalies in association with cognitive dysfunction and cerebral abnormalities (Waddington et al., 1995). Researchers have sought evidence of structural neuropathological alterations related to TD using several neuronimaging techniques. First, using CT, Bartels et al. found patients with TD were with significantly greater width of the third ventricle, greater bicaudate distance, smaller areas of caudate nucleus head and lenticular nucleus, compared with age- and sex-matched controls. They suggested that structural abnormalities, primarily in the basal ganglia system, are present in TD patients (Bartels and Themelis, 1983). Ueyama et al. also found a low density rate in the basal nucleus of a group of TD patients, which was significantly higher than that of non-TD patients (Ueyama et al., 1993). Similarly, Gold et al. found patients with TD had significantly smaller ventricular-brain ratios (VBRs) than controls, and suggested that the abnormal movements of TD may result from specific dysfunction within the motor circuits of the basal ganglia (Gold et al., 1991). Dalgalarrondo et al. also found that caudate left area reduction and left temporal sulci enlargement were the most important parameters that discriminated patients with TD from non-TD patients. In that study, caudate left area reduction and left temporal sulci enlargement correlated significantly with cumulative duration of psychiatric hospitalizations only among patients with TD. Dalgalarrondo et al. concluded that structural abnormalities in the caudate nucleus and temporal lobes of patients with TD were related to longer treatment with antipsychotics (Dalgalarrondo and Gattaz, 1994).

Similar findings have been reported with magnetic resonance imaging (MRI). Bartzokis et al. found that schizophrenia patients with TD had significantly shortened left caudate T2 relaxation times, compared to patients without TD. They suggested that T2 relaxation time shortening in the basal ganglia may be helpful for predicting the risk for TD (Bartzokis et al., 1990). In another study, the volumes of the caudate nuclei of patients with TD were significantly smaller than those of patients without TD and normal controls (Mion et al., 1991). Granholm et al. also showed that increased severity of TD was associated with shortened caudate T2 relaxation time, and motor-learning scores correlated with caudate T2 relaxation time (Granholm et al., 1993). However, other MRI studies showed negative results. Elkashef et al. reported that schizophrenic patients had significantly larger right and left globus pallidus and right putamen volumes than did comparison subjects; but without significant differences in the volume of these structures between patients with and without persistent TD (Elkashef et al., 1994). In a study by Buckley et al., schizophrenic patients showed prolonged T2 relaxation times in the right putamen and globus pallidus than did control subjects, but no significant difference in T2 values was found between patients with and without TD (Buckley et al., 1995). In Harvey's study, neither significant differences in T1 relaxation time of the basal ganglia (putamen, globus pallidus and the head of the caudate) were found between schizophrenic patients with and without TD (Harvey et al., 1991). Thus, the result of neuronimaging for TD is still controversial, and the specific pathophysiologic processes underlying movement disorders are still not completely understood (Casey, 2004).

Increasing evidence suggests that a disturbance in connections between different brain regions, rather than abnormalities within the separate regions themselves, is responsible for the clinical symptoms and cognitive dysfunctions observed in schizophrenia (Volkow et al., 1988). Impaired neuropsychological performance and related functional imaging and electrophysiological findings in patients with schizophrenia are considered as expressions of disturbed functional connectivity of microcircuits throughout the brain (Stephan et al., 2006), and most frequently reported for the frontotemporal, frontoparietal, corticothalamic, interhemispheric, and corticocerebellar circuits (Hanson and Gottesman, 2005; Winterer and Weinberger, 2004). This disturbed connectivity is related to alterations in the numbers, distribution, and ultrastructural integrity of oligodendrocytes of white matter (Hanson and Gottesman, 2005). Postmortem studies also identified abnormalities in the myelin sheath (Uranova et al., 2004), oligodendroglia (Hof et al., 2003), and interstitial neurons (Akbarian et al., 1996) in schizophrenic patients compared with healthy volunteers. Thus, new attention is turning to white matter (WM) fiber tracts, which subserve anatomical connections between distant, as well as proximal, regions of the brain (Kubicki et al., 2007).

Diffusion tensor imaging (DTI) is a useful tool for examining and quantifying the microstructure of WM, and provides information about its integrity by exploring water molecular anisotropy within each MRI voxel (Garver et al., 2007). In coherent fiber structure, diffusion of water is greater parallel to, rather than perpendicular to, axonal tracts and is termed "anisotropy." In general, water molecules are more restricted perpendicularly, and the anisotropy is high, with greater WM integrity. Fractional anisotropy (FA) is a normalized DTI index ranging from 0 (completely random) to 1 (completely unidirectional) (Lim and Helpern, 2002). Previous DTI studies have shown that schizophrenia is associated with significant FA reduction in the frontal thalamic cerebellar circuit (Okugawa et al., 2006), the left internal capsule, the left-hemisphere WM of posterior superior temporal gyrus (Szeszko et al., 2005), corpus callosum (Agartz et al., 2001) and middle cerebellar peduncle (Okugawa et al., 2005). The results supported that damaged brain microcircuitry might contribute to the pathophysiology of schizophrenia. However,

Table 1
Comparison of characteristics between TD, schizophrenia, and normal control groups.

Demographic variables	TD ($n=20$)	Schizophrenia ($n=20$)	Normal control ($n=20$)	Significance
Age (years)	41.5/10.1	40.5/9.3	41.2/10.1	N.S.[a]
Gender (male/female)	5/15	5/15	5/15	N.S.
Handedness (left/right)	0/20	0/20	0/20	N.S.
Age of onset (years)	25.8/6.7	29.5/9.6	–	N.S.
Duration of illness (years)	15.0/7.2	10.6/9.3	–	N.S.
Antipsychotic (atypical/conventional)	15/5	18/2	–	N.S.
Antipsychotic (CPZ equivalent dose)	428.0/234.3	430.0/213.6		N.S.
PANSS				
Total	63.4/11.2	54.8/13.7	–	$p=0.024$
Positive	14.1/4.3	12.6/4.9	–	N.S.
Negative	18.0/4.2	13.0/4.2	–	$p=0.001$
General	31.6/4.8	26.9/6.6	–	$p=0.027$
AIMS				
Total	10.4/5.6	0.1/0.3	–	$p<0.001$
Orofacial	6.4/3.6	0.1/0.2	–	$p<0.001$
Extremities	4.2/2.4	0.0/0.0	–	$p<0.001$
SAS	6.6/4.5	0.1/0.4	–	$p<0.001$

The variables are demonstrated as means/std.
[a] N.S., nonsignificant.

although many reports have shown abnormal WM among schizophrenia patients, none has investigated WM abnormality among patients with TD, who had involuntary movement and unusually high incidence of negative symptoms (Berry et al., 2007). Previous report showed progressive decrement in frontal lobe white matter volume were associated with greater negative symptom severity (Ho et al., 2003).

We designed the study to investigate WM abnormalities in patients with TD using DTI among 20 schizophrenia patients with TD (Schizophrenia with TD group), 20 age-, gender- and handedness-matched schizophrenic patients without TD (Schizophrenia without TD group), and 20 matched healthy subjects. We hypothesized that more prominent reduction in FA will be found in schizophrenic patients with TD for white matter circuit involved in movement control and negative symptoms.

2. Methods

2.1. Patients

The study was conducted in a Medical Center, Taipei Veterans General hospital in Taiwan. The study subjects were enrolled from patients in psychiatric department outpatient clinic and Day care unit. Twenty schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, or

Table 2
Areas with significantly decreased FA values in schizophrenia patients ($N=40$) compared with normal controls ($N=20$).

Cluster size (voxels)	Coordinates of the most significant voxel			*t*-score	Anatomical location	Nearest GM[a]
	x	*y*	*z*			
Right hemisphere						
171	32	−30	48	5.58	Parietal sub-cortical WM[b]	Precentral gyrus
514	10	12	46	3.80	Cingulate gyrus WM	
80	44	−2	24	3.40	Frontal sub-cortical WM	Inferior frontal gyrus
110	44	−66	14	3.24	Middle temporal, middle occipital gyrus WM	
89	6	−4	−2	4.22	Midbrain, extra-nuclear WM	Hypothalamus
143	12	54	−4	4.28	Medial, superior frontal gyrus WM	
1283	40	−40	−6	6.24	Temporal sub-cortical WM	Parahippocampal gyrus, clausrum
68	24	−6	−8	4.22	Sub-cortical, extra-nuclear WM	Lateral globus pallidus
Left hemisphere						
53	−42	−46	30	3.62	Parietal supramarginal gyrus WM	
105	−10	32	28	3.74	Medial frontal gyrus WM	Cingulate gyrus
158	−14	−42	20	3.25	Corpus callosum	
303	−28	−58	20	3.75	Temporal sub-cortical WM	Middle temporal gyrus
50	−34	32	−4	3.91	Inferior frontal gyrus WM	
102	−12	46	−6	4.41	Medial, superior frontal gyrus WM	
2251	−22	−6	−8	5.36	Sub-cortical, extra-nuclear WM	Lateral globus pallidus
58	−26	22	−18	4.00	Inferior frontal gyrus WM	Subcallosum gyrus
538	−12	−58	−46	4.41	Cerebellum tonsil and dentate	

Statistical criteria: p-value<0.005, cluster size >50 voxels.
[a] GM: gray matter.
[b] WM: white matter.

DSM-IV, criteria) patients with TD (Schizophrenia with TD group), 20 schizophrenia patients without TD (Schizophrenia without TD group), and 20 matched healthy subjects (normal control group) were recruited for the study. These three groups were matched for age, gender ratio and handedness. Schooler and Kane's Research Diagnostic Criteria were used to define TD: (1) moderate abnormal involuntary movement in one or more body areas, or (2) mild involuntary movements in two or more areas (Schooler and Kane, 1982). The healthy control subjects were interviewed using the Mini-International Neuropsychiatric Interview (MINI) to confirm no previous history of neurologic or psychiatric illness, and all had normal brain structure confirmed by MRI scans. Subjects were excluded if they had other Axis I psychiatric diagnosis, serious neurologic or endocrine disorders, any medical condition or treatment known to affect the brain, alcohol/substance misuse related disorders, or mental retardation defined according to DSM-IV criteria. The clinical ratings included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for severity of psychopathology, the Abnormal Involuntary Movement Scale (AIMS) (Munetz and Benjamin, 1988) for TD, and the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970), for extrapyramidal side effects. The clinical ratings were performed by Dr. Bai, who has years

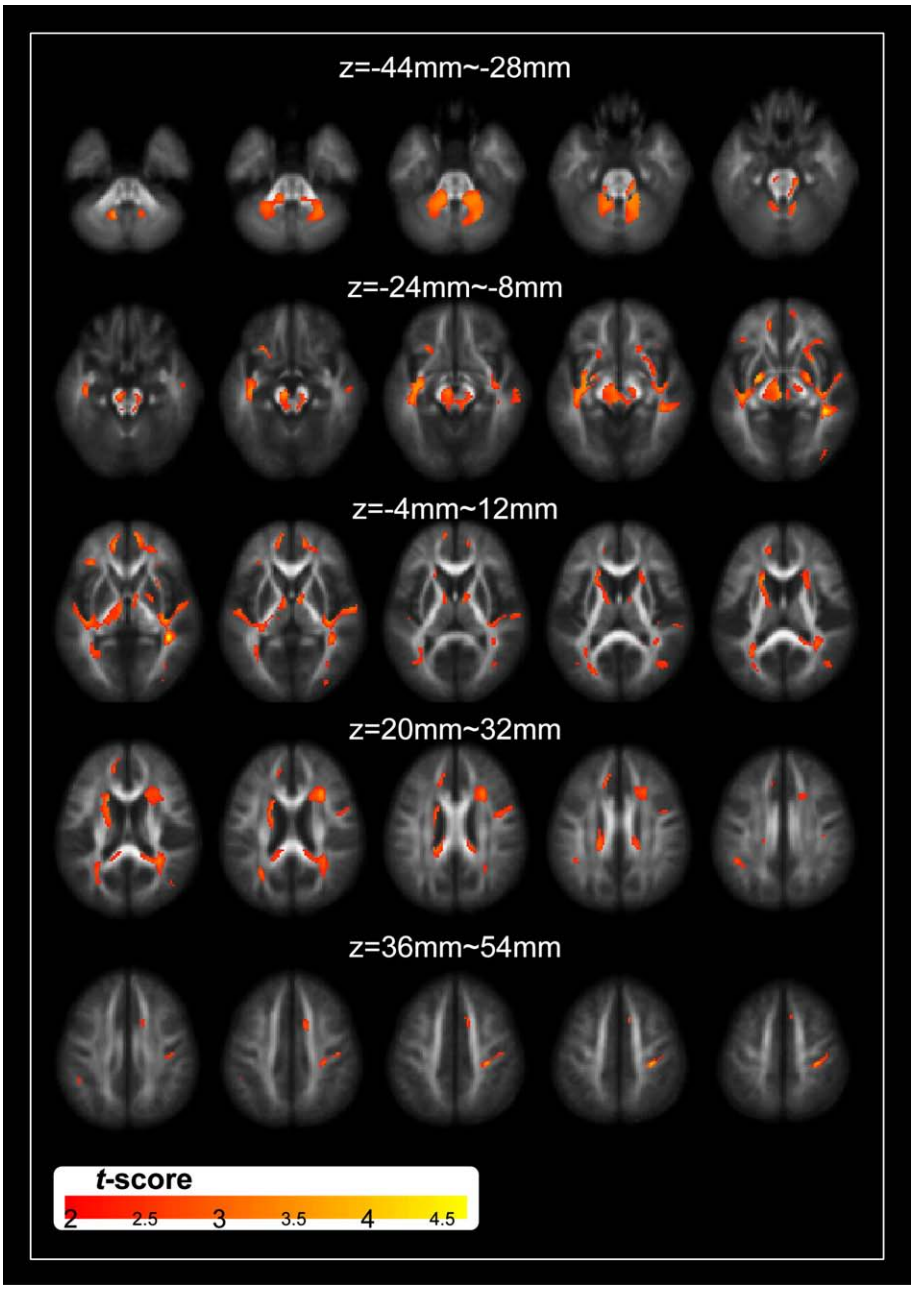


Fig. 1. Comparison of fractional anisotropy (FA) between schizophrenia patients ($N=40$) and normal control ($N=20$).

Table 3
Pearson correlation coefficients between clinical rating scores and FA values of clusters derived from the comparison of TD and schizophrenia groups.

	PANSS			AIMS			SAS total
	Positive	Negative	Total	Total	Orofacial	Extremities	
Right hemisphere							
Parietal sub-cortical WM *around precentral gyrus*	−0.129	−0.105	−0.159	0.002	−0.027	0.046	−0.128
Cingulate gyrus	−0.041	−0.227	−0.111	−0.247	−0.275	−0.106	−0.319
Frontal sub-cortical WM *around inferior frontal gyrus*	0.022	−0.025	−0.006	−0.062	−0.067	−0.032	−0.028
Middle temporal and middle occipital gyrus WM	0.200	−0.008	0.079	−0.172	−0.172	−0.066	−0.176
Midbrain, extra-nuclear WM *around hypothalamus*	0.081	−0.152	0.018	−0.037	−0.107	0.120	−0.015
Medial, superior frontal gyrus WM	−0.049	−0.243	−0.136	−0.115	−0.115	−0.083	−0.141
Temporal sub-cortical WM *around parahippocampal gyrus, clausrum*	−0.009	0.342	−0.207	−0.427	−0.409	−0.342	−0.289
Sub-cortical, extra-nuclear WM *around lateral globus pallidus*	0.019	−0.145	−0.014	−0.052	−0.081	−0.058	−0.030
Left hemisphere							
Parietal supramarginal gyrus WM	−0.143	−0.221	−0.214	−0.258	−0.267	−0.207	−0.315
Medial frontal gyrus WM *around cingulate gyrus*	−0.197	−0.516[a]	−0.345	−0.490	−0.475	−0.383	−0.344
Corpus callosum	0.188	−0.192	0.056	−0.313	−0.289	−0.287	−0.228
Temporal sub-cortical WM *around middle temporal gyrus*	0.173	−0.251	−0.001	−0.359	−0.320	−0.286	−0.327
Inferior frontal gyrus WM	0.017	−0.201	−0.029	−0.325	−0.278	−0.360	−0.171
Medial, superior frontal gyrus WM	−0.097	−0.298	−0.232	−0.213	−0.177	−0.176	−0.111
Sub-cortical, extra-nuclear WM *around lateral globus pallidus*	0.076	−0.211	−0.040	−0.153	−0.163	−0.162	−0.086
Inferior frontal gyrus WM *around subcallosum gyrus*	0.011	−0.307	−0.154	−0.411	−0.406	−0.248	−0.397
Cerebellum tonsil and dentate	0.057	−0.129	−0.016	−0.064	−0.074	−0.092	−0.040

Blom transformation was performed on the clinical rating scores except PANSS (positive, negative, and total) before the Pearson correlation coefficient analysis.
[a] Statistically significant, corrected p-value<0.05.

of experience using abnormal involuntary movement rating scales (AIMS) ratings for TD (Lin et al., 2008; Mo et al., 2007; Bai et al., 2003, 2005; Liou et al., 2005, 2006a,b, 2007; Chen et al., 2001). All procedures were approved by the institutional review board of Taipei Veterans General Hospital. Written informed consent was obtained from all subjects.

2.2. MRI procedures

All MR examinations were performed on a 1.5 T MR system (Excite II; GE Medical Systems, Milwaukee, Wis., USA) equipped with an 8-channel head coil in TPE-VGH. To diminish motion artifact generated during the scan, the subject's head was immobilized with cushions inside the coil after the alignment. One hundred twenty-four contiguous axial T1-weighted (T1W) images (slice thickness = 1.5 mm) were acquired parallel to the anterior–posterior commissure (AC–PC) through the whole head by applying a three-dimensional fluid-attenuated inversion-recovery fast spoiled-gradient recalled echo (FLAIR-FSPGR) acquisition sequence (TR = 8.548 ms, TE = 1.836 ms, TI = 400 ms, flip angle = 15°, field of view = 26 × 26 cm, matrix size = 256 × 256) to aid the localization of FA differences.

Fourteen diffusion tensor imaging volumes were obtained for each subject, including thirteen volumes with diffusion gradients applied along thirteen non-collinear directions (b = 900 s/mm^2) and one volume without diffusion weighting (b = 0). In the consideration of total brain coverage, each volume consisted of 70 contiguous axial slices (slice thickness = 2.2 mm) acquired parallel to the AC–PC by using a single shot spin-echo echo planar imaging (EPI) sequence (TR = 17,000 ms, TE = 68.9 ms, number of excitation = 6, field of view = 26 cm2, matrix size = 128 × 128). The total scanning

Table 4
Areas with significantly decreased FA values in schizophrenia without TD group (N = 20) compared with normal controls (N = 20).

Cluster size (voxels)	Coordinates of the most significant voxel			t-score	Anatomical location	Nearest GM[a]
	x	y	z			
Right hemisphere						
270	32	−30	50	4.47	Parietal postcentral gyrus WM[b]	
					Frontal sub-gyral WM	Cingulate gyrus, insula
183	28	−52	32	3.75	Temporal sub-cortical, extra-nuclear WM	Middle temporal gyrus
90	34	−20	−4	4.00	External capsule	Putamen
52	40	−40	−6	4.35	Temporal sub-cortical WM	Fusiform gyrus
51	24	−8	−8	3.90	Temporal Sub-cortical, extra-nuclear WM	Amygdala
Left hemisphere						
1306	−4	−14	−6	4.25	Brain stem	Mid-brain, pons
325	−12	−48	−34	3.85	Cerebellar tonsil	
242	−22	−6	−8	4.71	Temporal sub-cortical WM	Fusiform gyrus, Globus pallidus

Statistical criteria: p-value<0.005, cluster size >50 voxels.
[a] GM: gray matter.
[b] WM: white matter.

time to collect the entire T1-weighted and diffusion-weighted images took approximately 32 min for each subject.

2.3. Imaging processing

The FA maps for each subject were computed by using in-house program and registered to the ICBM 152 template (Montreal Neurological Institute) which was derived from 152 normal subjects and approximated the Talairach space by three steps. First, concerning reducing the error term resulted from image registration and bias in template selection, a specific customized group template was created in the study. This involved spatially normalizing each structural MR images to the ICBM 152 template. The optimum 12-parameter affine transformation was used in this step. All the normalized T1W images were then averaged and smoothed with an isotropic 8-mm full-width at half maximum (FWHM) Gaussian kernel, and the customized template was created. Second, non-diffusion weighted ($b=0$) images of an individual subject were co-registered to their T1W images based on normalized mutual information as the cost function. The registration parameters were subsequently applied on the FA maps which are inherently registered to other diffusion-weighted images during the acquisition. In addition, these FA maps were skull-

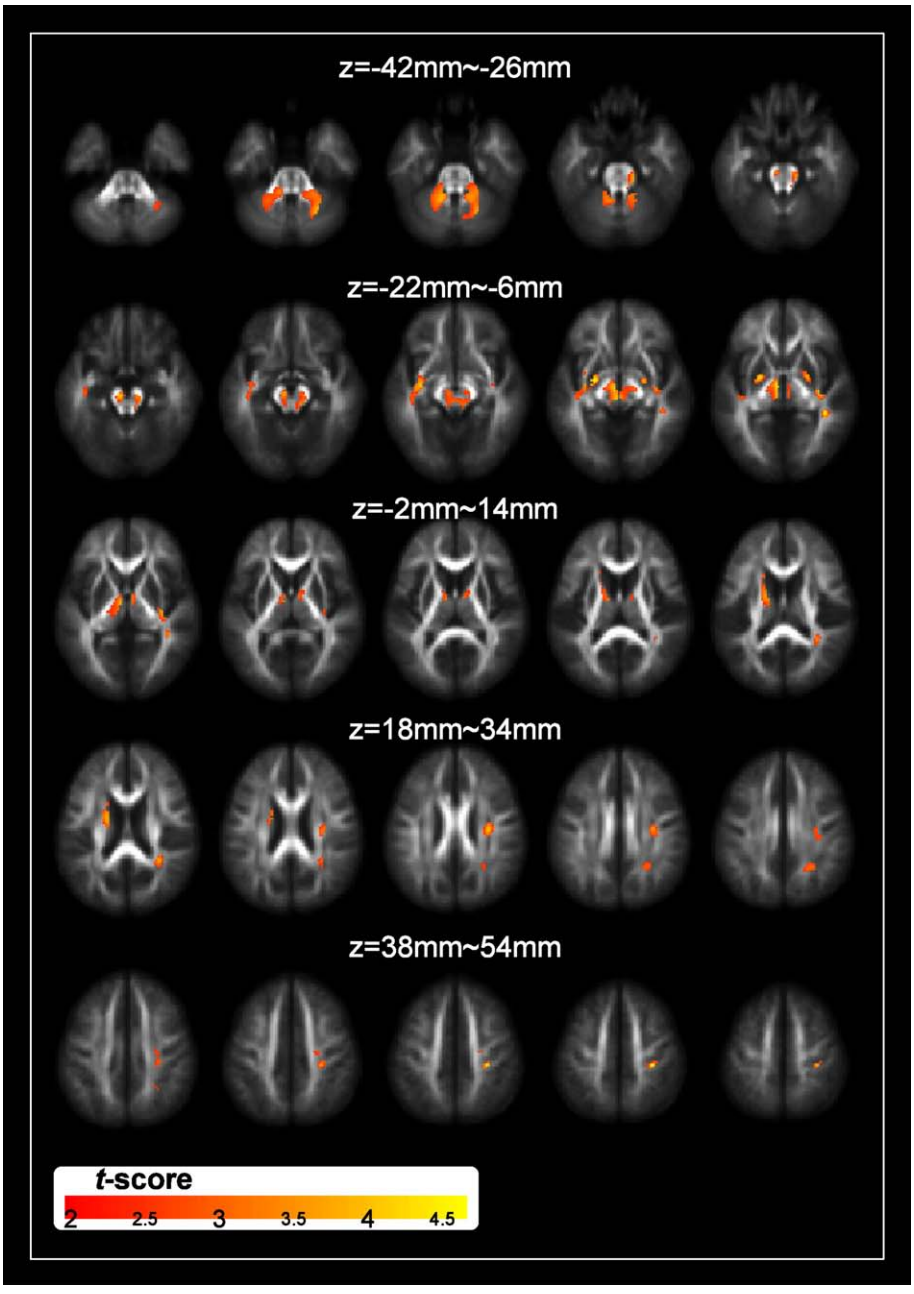


Fig. 2. Comparison of fractional anisotropy (FA) between Schizophrenia without TD group ($N=20$) and normal control ($N=20$).

stripped to remove non-brain tissue and background noise by utilizing Brain Extraction Tool (BET) compiled in FSL library 3.3 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University, Oxford, UK). Third, all the 60 T1W scans were transformed to the same stereotactic space as the customized template image by applying an affine transformation with 12 degrees of freedom together with a series of non-linear warps characterized by a set of $7\times8\times7$ basis functions. The transformation parameters derived from this step were also applied to the FA maps, thus the FA maps were effectively registered to the MNI space.

Since DTI was sensitive to the alterations in white matter (WM), a customized WM mask threshold at 0.4 was used for statistical mapping analysis as an explicit mask, which would ensure the statistical comparisons focusing on the WM tissues. All the image processing including images registration, spatial normalization, customized template creation, segmentation, and voxel-wise statistical comparisons were manipulated using Statistical Parametric Mapping 2 (SPM2) (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB6.5 (MathWorks, MA).

2.4. Statistical analyses

1. Descriptive statistics, means, SDs, and percentages were used for continuous variables and categorical variables, respectively. A voxel-based one-way analysis of variance (ANOVA) on WM area was performed with SPM2 to investigate the FA differences among the groups. First, we compared the differences in FA maps between the 40 schizophrenia patients (with and without TD) and the normal control group. Second, we compared the differences in FA maps among the three groups: 1. Schizophrenia without TD group/normal control group, 2. Schizophrenia with TD group/normal control group; and 3. Schizophrenia without TD group/Schizophrenia with TD group. To control the factors of age at onset of illness, duration of illness, and antipsychotic chlorpromazine (CPZ) equivalent dose, the voxel-based multiple analysis of covariance (MANCOVA) was performed with SPM2 to investigate the FA differences between patients groups. In post-hoc tests, six contrasts were used to detect where each voxel had a higher or lower fractional anisotropy when comparing each two of the three groups. FA differences were deemed to be significant at the individual voxel level when p-value less than 0.005 and extended cluster size more than 50 voxels. Furthermore, we investigate the relationships between the clinical rating scales and the mean FA values of clusters derived from the comparison between groups with Blom transformation. Pearson's correlation coefficient tests were performed with SPSS 13.0 (SPSS Inc, Chicago; IL, USA). The p-value less than 0.01 was deemed as significant linear correlation between two independent variables.

3. Results

The study subjects were 20 schizophrenia patients with TD (Schizophrenia with TD group), 20 age-gender- and all right-handedness matched schizophrenia patients without TD (Schizophrenia without TD group), and 20 healthy subjects (normal control group). No significant difference in the age at onset of illness, duration of illness, antipsychotic chlorpromazine (CPZ) equivalent dose, or class of antipsychotics were noted between the Schizophrenia with and without TD groups (Table 1). All patients received only one antipsychotic. The use of antipsychotics for patients in Schizophrenia with TD group were Clozapine ($n=4$), Aripiprazole ($n=3$), Risperidone ($n=7$), Haloperidol ($n=1$), Olanzapine ($n=1$), Flunarizine ($n=1$), Flupenthixol ($n=1$), Chloropromazine ($n=1$), and Sulpiril ($n=1$). The use of antipsychotics for patients in Schizophrenia without TD group were Sertindole ($n=1$), Ziprasidone ($n=2$), Risperidone ($n=3$), Aripiprazole ($n=9$), Flunarizine ($n=1$), Clozapine ($n=2$), Haloperidol ($n=1$) and Olanzapine ($n=1$). The TD group had significantly higher PANSS total scores ($p=0.024$), negative ($p=0.001$) and

Table 5
Areas with significantly decreased FA values in Schizophrenia with TD group ($N=20$) compared with normal controls ($N=20$).

Cluster size (voxels)	Coordinates of the most significant voxel			t-score	Anatomical location	Nearest GM [a]
	x	y	z			
Right hemisphere						
1805	40	−40	−6	7.03	Temporal sub-cortical, extra-nuclear WM (basal ganglia) [b] Temporal sub-cortical WM	Caudate tail Fusiform gyrus
567	28	20	22	4.71	External capsule	Caudate nuclear
567	8	−44	−34	4.03	Brain stem Cerebellum dentate, tonsil	Mid-brain, pons
201	12	54	−4	4.28	Frontal sub-gyral WM Medial, Superior frontal gyrus	Anterior cingulate gyrus
143	32	−30	48	5.25	Parietal postcentral gyrus WM	
103	2	−2	−4	4.68	Sub-cortical, extra-nuclear WM	Lateral globus pallidus
Left hemisphere						
2935	−38	−18	−18	5.42	Temporal sub-cortical, extra-nuclear WM (basal ganglia)	Putamen, caudate tail
457	−10	32	28	4.98	Frontal cingulate gyrus WM	
413	−10	−42	−38	3.78	Cerebellum Tonsil	
104	−42	−48	30	3.97	Parietal supramarginal gyrus WM	
99	−32	32	−4	4.60	Middle, inferior frontal gyrus WM	

Statistical criteria: p-value<0.005, cluster size >50 voxels.
[a] GM: gray matter.
[b] WM: white matter.

general psychopathology scales ($p=0.027$), AIMS ($p<0.001$) and SAS scores ($p<0.001$) (Table 1). AIMS scores were positively correlated with PANSS negative scores ($r=0.425$; $p=0.019$), and SAS scores ($r=0.646$; $p<0.001$).

First, we compared differences in FA maps between the 40 schizophrenia patients (Schizophrenia with and without TD groups combined) and the normal control group. The schizophrenia patients were with significantly wide spread lower FA than the normal control group (Table 2, Figs. 1, 5-1). The correlation between the clinical rating scales and the mean FA values of clusters derived from the comparison between schizophrenia patients and normal control group were performed with Blom transformation. The results showed only AIMS total score was negatively correlated with FA value over temporal sub-cortical WM, and no significant correlations were noted between other clinical ratings and FA values (Table 3).

Then we compared the FA among three groups:

1. Schizophrenia without TD group and normal control group: significantly lower fractional anisotropy (FA) were noted in the temporal subcortical WM, parietal postcentral gyrus WM and frontal subgyral WM, and temporal sub-cortical WM (Table 4; Figs. 2, 5-2).

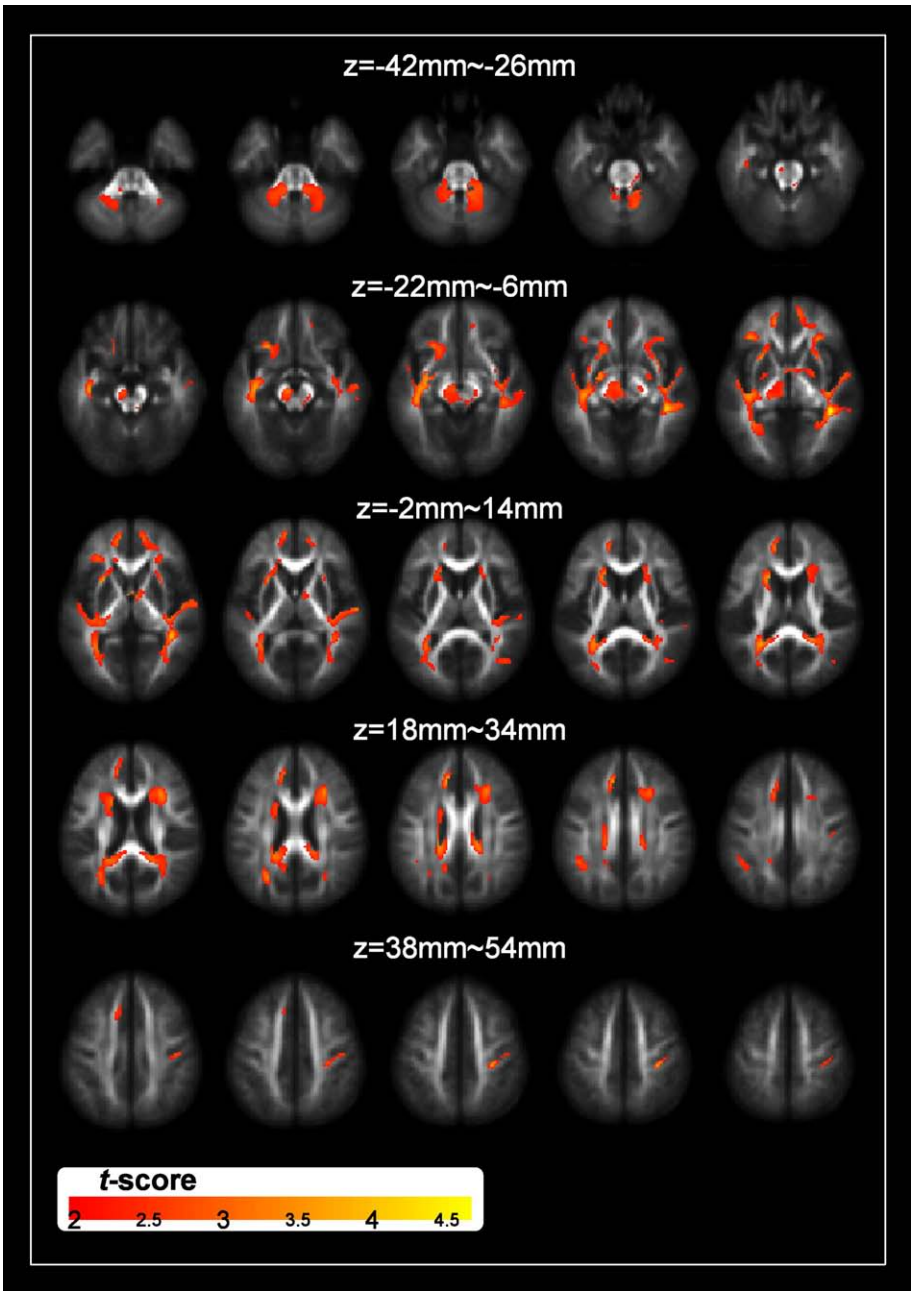


Fig. 3. Comparison of fractional anisotropy (FA) between Schizophrenia with TD group ($N=20$) and normal control ($N=20$).

2. Schizophrenia with TD group and normal control group: significantly much more widespread lower FA over temporal sub-cortical, extra-nuclear WM, parietal post-central gyrus WM, frontal cingulate gyrus WM, sub-cortical, extra-nuclear WM, external capsule, and middle, inferior frontal gyrus WM (Table 5, Figs. 3, 5-3).
3. Schizophrenia with TD group and Schizophrenia without TD group: significantly lower FA over the inferior frontal gyrus and temporal sublobar extranuclear WM (around the basal ganglion), parietal precuneus gyrus WM (around somato-sensory cortex), and medial frontal gyrus WM (around dorsolateral prefrontal cortex) (Table 6, Figs. 4, 5-4). The comparison was adjusted with control of age, duration of illness, and antipsychotic chlorpromazine (CPZ) equivalent dose. Then we investigated the relationships between the clinical rating scales of the 40 schizophrenia patients and these decreased FA values. The AIMS and SAS score were positively correlated with decreased FA over inferior frontal gyrus WM ($p<0.01$), temporal sublobar extranuclear WM (around basal ganglion and middle temporal gyrus) ($p<0.01$), parietal precuneus gyrus WM (around somato-sensory cortex) ($p<0.01$), medial frontal gyrus WM (around dorsolateral prefrontal cortex) ($p<0.01$), and frontal sub-cortical WM ($p<0.01$). The PANSS negative score, AIMS total score and SAS score positively correlated with decreased FA over the medial frontal gyrus WM (around dorsolateral prefrontal cortex) ($p<0.01$) (Table 7; Fig. 6). The multivariate analyses showed only PANSS negative scores was the only significant factor related to FA over medial frontal gyrus WM (around dorsolateral prefrontal cortex) with control of AIMS total scores, and SAS scores.

4. Discussion

Our study results showed that schizophrenia patients without TD had significantly lower FA over temporal subcortical WM, parietal postcentral gyrus WM and frontal subgyral WM compared with normal controls. The result was consistent with previous results (Okugawa et al., 2006; Szeszko et al., 2005), and supported the hypothesis that damaged brain microcircuits of WM might contribute to the pathophysiology of schizophrenia. Our results further demonstrated that the Schizophrenia with TD group had more widespread FA decreases than schizophrenia without TD group, especially involved temporal sub-cortical, extra-nuclear WM, parietal postcentral gyrus WM, frontal cingulate gyrus WM, sub-cortical, extra-nuclear WM, external capsule, and middle, inferior frontal gyrus WM. The widespread WM abnormality may be related to the more severe psychopathology of the Schizophrenia with TD group than that of the Schizophrenia without TD group, as underscored by their significantly higher PANSS total, negative and general psychopathology scores. The result was consistent with many previous reports that schizophrenia patients with TD were associated with more severe clinical psychopathology than those without TD (Miller et al., 2005; Ascher-Svanum et al., 2008; Eberhard et al., 2006; Bhatia et al., 2004; Gebhardt et al., 2008). Dyskinesia and psychopathology are in some respects related to each other (Gebhardt et al., 2008) and worsening overall psychopathology in schizophrenia is longitudinally associated with the emergence of TD (Tenback et al., 2007). Cortese et al. suggested that the positive association of the severity of dyskinesia and a psychotic syndrome indicated the neuromotor disturbances may be a core feature of schizophrenia in a substantial proportion of patients, and implicates multiple frontostriatal circuits regulating limbic and neuromotor behavior in schizophrenia (Cortese et al., 2005). Previous reports showed that brain atrophy and greater sulcal enlargement was increased in patients with TD as a result of grey matter changes (McCreadie et al., 2002). Our study is the first to show diffuse abnormality of white matter associated with TD.

While we compared the difference of FA maps between 40 schizophrenia patients (Schizophrenia patients with and without TD groups combined) and normal control, the results showed wide spread FA decreases over many clusters. And most clinical ratings were not correlated with decreased FA over these areas, except AIMS total score was correlated with decreased FA over temporal sub-cortical WM. The results indicated these identified clusters from comparison of 40 schizophrenia patients and normal control group were not specific to the circuits related to TD. So we directly compared

Table 6
Areas with significantly decreased FA values in Schizophrenia with TD group ($N=20$) compared to Schizophrenia without TD group ($N=20$) (with control of age, duration of illness and antipsychotic chlorpromazine equivalent dose).

Cluster size (voxels)	Coordinates of the most significant voxel			*t*-score	Anatomical location	Nearest GM [a]
	x	*y*	*z*			
Right hemisphere						
191	34	−48	−4	4.14	Para-hippocampal gyrus WM [b]	
91	22	−66	30	4.02	Parietal precuneus gyrus WM	Somatosensory cortex
Left hemisphere						
199	−26	12	−2	5.37	Inferior frontal gyrus WM	Putamen
297	−28	−48	8	5.41	Temporal sub-cortical, extra-nuclear WM	Basal ganglia
84	−26	−64	24	4.54	Temporal sub-cortical, extra-nuclear WM	Middle temporal gyrus
89	−12	32	32	3.91	Medial frontal gyrus WM	Dorsolateral prefrontal cortex
79	−22	0	30	3.11	Frontal sub-cortical WM	

Statistical criteria: *p*-value<0.005, cluster size >50 voxels.
[a] GM: gray matter.
[b] WM: white matter.

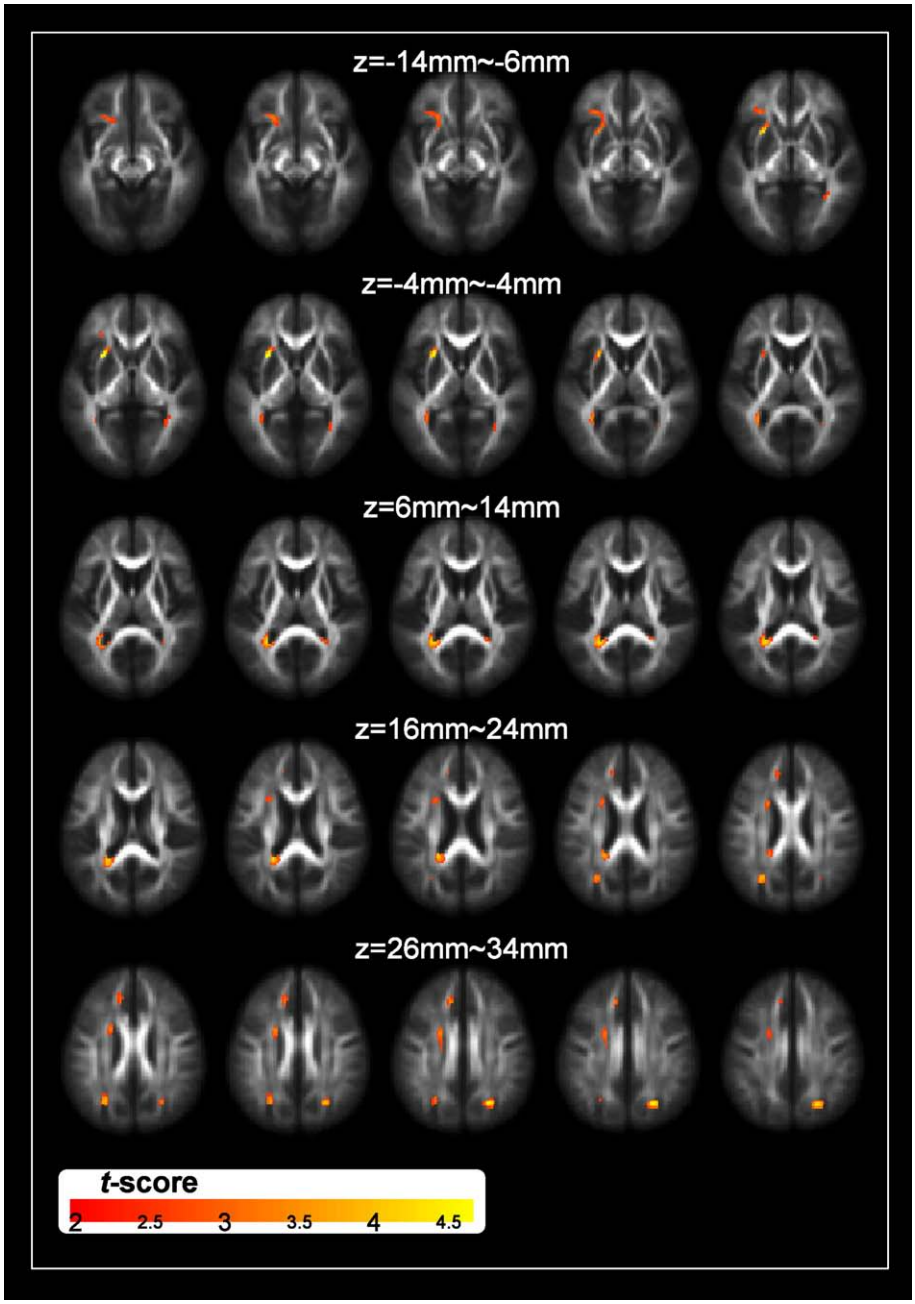


Fig. 4. Comparison of fractional anisotropy (FA) between Schizophrenia without TD group ($N=20$) and Schizophrenia with TD group ($N=20$).

the Schizophrenia with TD and Schizophrenia without TD groups to explore the specific dysfunctional circuits for abnormal involuntary movements. The Schizophrenia with TD group showed significantly more FA decrease over the inferior frontal gyrus (around the putamen) and temporal sublobar extranuclear WM (around the basal ganglion), parietal precuneus gyrus WM (around somatosensory cortex), and medial frontal gyrus WM (around dorsolateral prefrontal cortex). Furthermore, the AIMS and SAS scores were positively correlated with decreased FAs over almost all identified clusters. And the AIMS scores were positively correlated with SAS scores. These results supported previous findings that neuroleptic-induced EPS is the most important risk factor for developing TD (Miller et al., 2005; McCreadie et al., 2005; Tenback et al., 2006; Ascher-Svanum et al., 2008). According to the current model of basal ganglia function, cortical information is processed in the basal ganglia nuclei, which in turn send projections back via the thalamus to the cortex (corticobasal ganglion loop) (Alexander and Crutcher, 1990). The striatum is the main entry point of cortical information to the basal ganglia, and it receives afferents from anatomically and functionally different areas of the

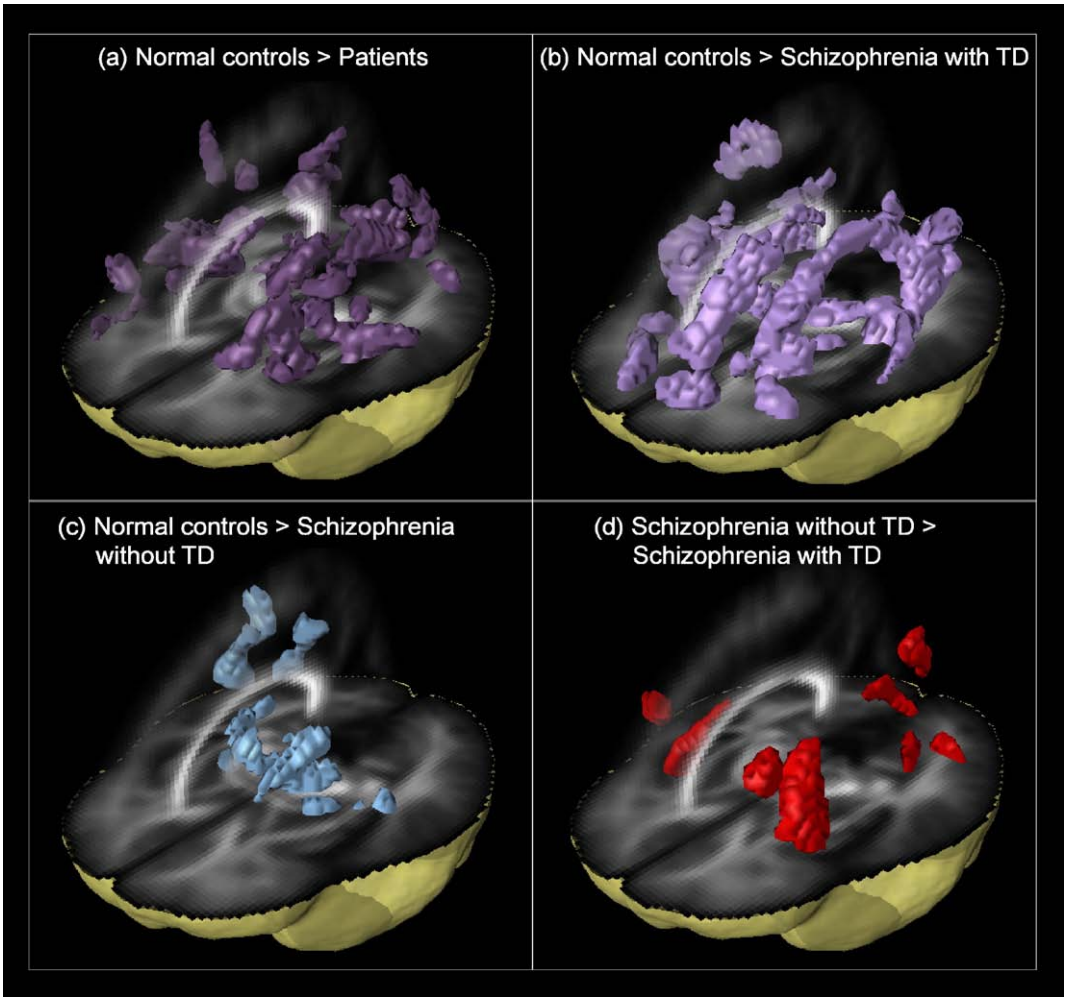


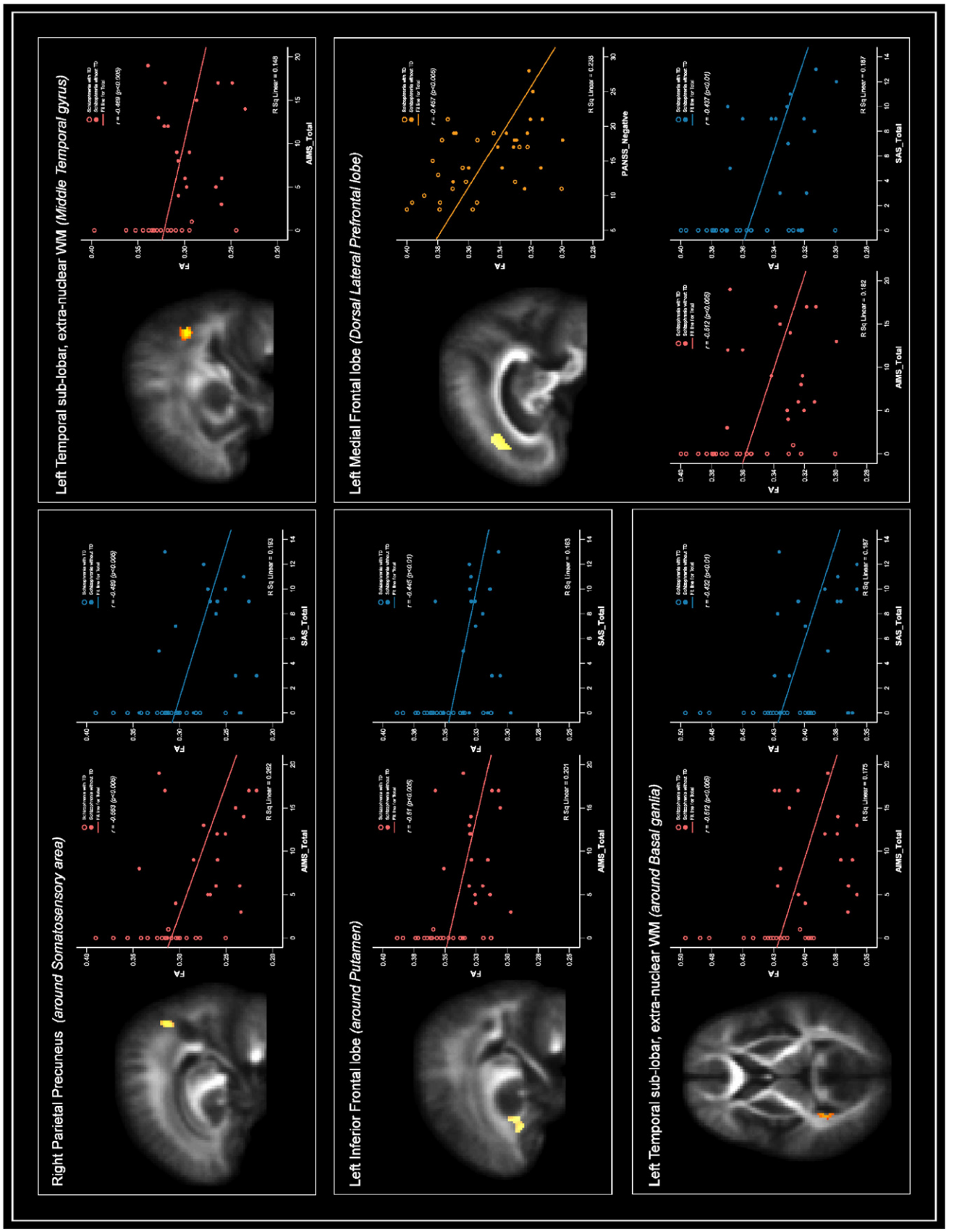
Fig. 5. 3D surface rendering of the outcome clusters superimposed on the averaged FA image.

cerebral cortex. Leh et al. used DTI tractography to reconstruct neural connections between the frontal cortex, caudate nucleus, and putamen. They found that the caudate nucleus is interconnected with the prefrontal cortex, inferior and middle temporal gyrus, frontal eye fields, cerebellum and thalamus. The putamen is interconnected with the prefrontal cortex, primary motor area, primary somatosensory cortex, supplementary motor area, premotor area, cerebellum and

Table 7
Pearson correlation coefficients between clinical rating scores and FA values of clusters derived from the comparison of Schizophrenia with and without TD groups ($N = 40$).

	PANSS			AIMS			SAS total
	Positive	Negative	Total	Total	Orofacial	Extremities	
Right hemisphere							
Parietal precuneus gyrus WM *around somatosensory cortex*	−0.198	−0.273	−0.236	−0.563**	−0.516**	−0.496**	−0.489**
Para-hippocampal gyrus WM	0.066	−0.121	0.015	−0.390	−0.361	−0.308	−0.298
Left hemisphere							
Inferior frontal gyrus WM *around putamen*	0.019	−0.327	−0.129	−0.510**	−0.464**	−0.423*	−0.445*
Temporal sub-cortical, extra-nuclear WM *around basal ganglia*	0.152	−0.144	0.083	−0.512**	−0.464**	−0.451**	−0.432*
Temporal sub-cortical, extra-nuclear WM *around middle temporal gyrus*	−0.004	−0.105	−0.006	−0.469**	−0.424*	−0.386	−0.340
Medial frontal gyrus WM *around dorsolateral prefrontal cortex*	−0.204	−0.457**	−0.316	−0.512**	−0.530**	−0.372	−0.437*
Frontal sub-cortical WM	0.117	−0.313	0.016	−0.488**	−0.484**	−0.430*	−0.375

Blom transformation was performed on all the clinical rating scores before the Pearson correlation coefficient analysis.
** Statistically significant, p-value < 0.005.
* Statistically significant, p-value < 0.01.


Left Temporal sub-lobar, extra-nuclear WM (Middle Temporal gyrus)
Left Medial Frontal lobe (Dorsal Lateral Prefrontal lobe)
Right Parietal Precuneus (around Somatosensory area)
Left Inferior Frontal lobe (around Putamen)
Left Temporal sub-lobar, extra-nuclear WM (around Basal ganlia)
FA
AIMS_Total
SAS_Total
PANSS_Negative
Schizophrenia with TD
Schizophrenia without TD
Pt's low FA Total
R Sq Linear = 0.148
R Sq Linear = 0.262
R Sq Linear = 0.163
R Sq Linear = 0.201
R Sq Linear = 0.238
R Sq Linear = 0.182
R Sq Linear = 0.175
R Sq Linear = 0.187

thalamus, which explained the involvement of the putamen in motor functions and movement disorders, as a 'sensorimotor circuit' (Leh et al., 2007). Electrophysiological studies have also shown many functional similarities between basal ganglia and the cortical areas to which they are connected, suggesting that a similar activation pattern may be expected in cortical and related basal ganglia areas (Schultz et al., 2000). The basal ganglion and frontal cortex (corticobasal ganglion loop) are thought to be involved in the buildup of sequential motor behavior from movement elements, as well as in goal-directed behavior, in learning related to motor and cognitive action plans, and in action-planning itself or its neuromodulation. Therefore, disruption of these corticobasal ganglion circuits could account for both the negative symptom and movement disorders (Graybiel, 1997). Our results showed that patients with TD had more widespread FA decreases, especially involving abnormality of WM around the basal ganglion and frontal cortex. This finding correlated the severity of dyskinesia and negative symptoms may support the hypotheses regarding corticobasal ganglion circuit dysfunction related to the pathophysiology of TD.

Importantly, we also found the decreased FA over medial frontal gyrus WM positively correlated with PANSS negative scores. And the AIMS scores were also positively correlated with PANSS negative scores. Schizophrenia patients with TD had been reported with an unusually high incidence of negative symptoms (Berry et al., 2007; Wonodi et al., 2005; Gebhardt et al., 2008; Chouinard, 2006; Pantelis et al., 2001). Studies examining the relationship between tardive dyskinesia, negative symptoms, and impaired cognitive function have generally found significant associations (Brown and White, 1991). Pantelis et al. suggested that tardive dyskinesia and negative symptoms are markers of compromise of the cerebral systems that mediate spatial working memory. They hypothesized candidate neural circuits include the frontal–striatal–thalamic systems, particularly those involving the dorsolateral prefrontal cortex (Pantelis et al., 2001). Our result was the first image study to support their hypothesis and TD may be an epiphenomenon for the damaged brain microcircuits.

The pathophysiology of neuroleptic-induced TD remains to be fully understood. The leading hypothesis involves dopamine receptor hypersensitivity, and is supported by neuroleptic-induced EPS as the most important risk factor (Miller et al., 2005; Tenback et al., 2006). Longitudinal studies suggest that conventional antipsychotic medication may enlarge the basal ganglion (Gur et al., 1998; Shihabuddin et al., 1998; Keshavan et al., 1998). The effect of antipsychotics on neuroanatomical changes to the basal ganglion may be the result of a dopamine D1 and dopamine D2 receptor blockade, which causes activation, regeneration, and hypertrophy of striatal synaptic and/or cellular elements. Hypermetabolism of these specific brain regions are suggested to be associated with vulnerability to TD development (Szymanski et al., 1996). Significant correlations between dosages of antipsychotics and WM volume over caudate nucleus (Takase et al., 2004), and FA values over left frontal WM (Minami et al., 2003), and middle cerebellar peduncles (Okugawa et al., 2004) have been reported in schizophrenia patients. These findings support the view that long-term antipsychotic treatment may cause volume change of basal ganglion and related abnormality of WM. Another important pathophysiologic theory of TD involves neurotoxicity (Zhang et al., 2007). Dopamine is metabolized by monoamine oxidase to dihydroxyphenylacetic acid; a byproduct of this reaction is hydrogen peroxide. Free radicals may be involved in the pathogenesis of TD. The potent antioxidants vitamin E, Vitamin B6, and piracetam have been shown to alleviate the severity of TD in randomized double-blind, placebo-controlled studies (Lerner et al., 2007; Libov et al., 2007). These studies support the neurotoxicity hypothesis. Cerebral white matter, composed of myelin-containing oligodendrocytes, is highly sensitive to excitotoxicity (Christensen et al., 2004). These lead to the possibility that antipsychotic medications might influence the pruning, disconnection, or imperfect repair of WM in such a way as to cause changes in anisotropy. Swelling of myelin and of WM, associated interference with the speed of neurotransmission through myelinated axons, and dysynchrony of information-processing by subcortical and cortical networks may be associated with development of TD.

To the best of our knowledge, this is the first study examining white matter integrity in schizophrenia patients with tardive dyskinesia. We suggest that misconnection of neural fibers over the basal ganglion and frontal gyrus WM may be related to the presence of TD in schizophrenia patients. However, several limitation of the study should be addressed. First, patients with TD enrolled in the study are with more severe psychopathology, and the result was consistent with many previous reports. But due to the cross-section design, it is not possible to attribute the findings of white matter change to TD per se and to separate TD from the context of the illness of schizophrenia. Second, we do not as yet know whether the abnormalities observed to date reflect a decrease in number of axons, decreased axonal diameter, thinner myelination sheaths, less coherent fibers, or more fiber crossings(Kubicki et al., 2007). Thus, the issue of cause or consequences can't be answered, and further prospective studies are required. Third, the patients in TD and schizophrenia groups were with more than 10 years of illness duration, it's difficult to get all the medical records of previous medications, including type of antipsychotics, duration, and accumulated dosages. But all of these factors may relate to the white matter changes. Fourth, most of the patients received atypical antipsychotics while being enrolled in the study, but all antipsychotics show different risk of inducing EPS and tardive dyskinesia. However, because the limited case number for each antipsychotic, it's difficult to compare the difference of FA among different antipsychotic with enough statistic power. The effects of different antipsychotics on the white matter abnormality need further larger scaled researches. Finally, generalizations from the study were limited by the small number of subjects, more large scale studies are required to validate the results.

Fig. 6. Correlation between clinical rating score of schizophrenia patients ($N = 40$) and fractional anisotropy (FA) values of clusters derived from the comparison of Schizophrenia with TD group and Schizophrenia without TD group.

Role of the funding source

Funding for this study was provided by National Science Council, Taiwan and Taipei Veterans General Hospital, Taiwan; the National Science Council and Taipei Veterans General Hospital had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Dr. Ya Mei Bai: collect the subjects and clinical rating, wrote the protocol, conducted the analysis and wrote the article.

Mr. Kun-Hsien Chou, and Miss I-Yun Chen: conducted the MRI procedures for all subjects and analyzed the data of Diffusion Tensor Image.

Dr. Cheng-Ta Li, and Dr. Kai Chun Yang: collected the subjects, reference search and gave the idea for study design.

Dr. Yuan-Hwa Chou: gave the critical comment for the study design.

Professor Tung-Ping Su and Dr: coordinate the clinical research team, gave the critical comment for the study design and writing of the article, as the corresponding author for the clinical part.

Professor Ching-Po Lin: coordinate the Image team, all technique support, and Image data analysis, as the corresponding author for Image part.

All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

Acknowledgements

The study was supported by grants from the National Science Council, Taiwan (NSC 96-2314-B-075-009 and NSC 97-2752-B-075-001-PAE), and Taipei Veterans General Hospital (V97C1-061 and V97ER1-003).

References

Agartz, I., Andersson, J.L., Skare, S., 2001. Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. NeuroReport 12, 2251–2254.

Akbarian, S., Kim, J.J., Potkin, S.G., Hetrick, W.P., Bunney, W.E., Jones, E.G., 1996. Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. Arch. Gen. Psychiatry 53, 425–436.

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 266–271.

Ascher-Svanum, H., Zhu, B., Faries, D., Peng, X., Kinon, B.J., Tohen, M., 2008. Tardive dyskinesia and the 3-year course of schizophrenia: results from a large, prospective, naturalistic study. J. Clin. Psychiatry e1–e9.

Bai, Y.M., Yu, S.C., Lin, C.C., 2003. Risperidone for severe tardive dyskinesia: a 12-week randomized, double-blind, placebo-controlled study. J. Clin. Psychiatry 64, 1342–1348.

Bai, Y.M., Yu, S.C., Chen, J.Y., Lin, C.Y., Chou, P., Lin, C.C., 2005. Risperidone for pre-existing severe tardive dyskinesia: a 48-week prospective follow-up study. Int. Clin. Psychopharmacol. 20, 79–85.

Bartels, M., Themelis, J., 1983. Computerized tomography in tardive dyskinesia. Evidence of structural abnormalities in the basal ganglia system. Arch. Psychiatr. Nervenkr. 233, 371–379.

Bartzokis, G., Garber, H.J., Marder, S.R., Olendorf, W.H., 1990. MRI in tardive dyskinesia: shortened left caudate T2. Biol. Psychiatry 28, 1027–1036.

Berry, K., Drake, R., Stewart, C., Aitkin, L.M., Byrne, J., Barrowclough, C., Purandare, N., 2007. Orofacial dyskinesia, frontal lobe dysfunction, and coping in older people with psychosis. Am. J. Geriatr. Psychiatry 15, 800–806.

Bhatia, T., Sabeeha, M.R., Shriharsh, V., Garg, K., Segman, R.H., Uriel, H.L., Strous, R., Nimgaonkar, V.L., Bernard, L., Deshpande, S.N., 2004. Clinical and familial correlates of tardive dyskinesia in India and Israel. J. Postgrad. Med. 50, 167–172.

Brown, K.W., White, T., 1991. The association among negative symptoms, movement disorders, and frontal lobe psychological deficits in schizophrenic patients. Biol. Psychiatry 30, 1182–1190.

Buckley, P., O'Callaghan, E., Mulvany, F., Larkin, C., Stack, J.P., Redmond, O., Ennis, J.T., Thompson, P., Waddington, J.L., 1995. Basal ganglia T2 relaxation times in schizophrenia: a quantitative magnetic resonance imaging study in relation to tardive dyskinesia. Psychiatry Res. 61, 95–102.

Casey, D.E., 2004. Pathophysiology of antipsychotic drug-induced movement disorders. J. Clin. Psychiatry 65 (Suppl 9), 25–28.

Chen, J.Y., Bai, Y.M., Pyng, L.Y., Lin, C.C., 2001. Risperidone for tardive dyskinesia. Am. J. Psychiatry 158, 1931–1932.

Chouinard, G., 2006. Interrelations between psychiatric symptoms and drug-induced movement disorder. J. Psychiatry Neurosci. 31, 177–180.

Christensen, J., Holcomb, J., Garver, D.L., 2004. State-related changes in cerebral white matter may underlie psychosis exacerbation. Psychiatry Res. 130, 71–78.

Correll, C.U., Schenk, E.M., 2008. Tardive dyskinesia and new antipsychotics. Curr. Opin. Psychiatry 21, 151–156.

Cortese, L., Caligiuri, M.P., Malla, A.K., Manchanda, R., Takhar, J., Haricharan, R., 2005. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. Schizophr. Res. 75, 65–75.

Dalgalarrondo, P., Gattaz, W.F., 1994. Basal ganglia abnormalities in tardive dyskinesia. Possible relationship with duration of neuroleptic treatment. Eur. Arch. Psychiatry Clin. Neurosci. 244, 272–277.

Eberhard, J., Lindstrom, E., Levander, S., 2006. Tardive dyskinesia and antipsychotics: a 5-year longitudinal study of frequency, correlates and course. Int. Clin. Psychopharmacol. 21, 35–42.

Elkashef, A.M., Buchanan, R.W., Gellad, F., Munson, R.C., Breier, A., 1994. Basal ganglia pathology in schizophrenia and tardive dyskinesia: an MRI quantitative study. Am. J. Psychiatry 151, 752–755.

Garver, D.L., Holcomb, J.A., Christensen, J.D., 2007. Compromised myelin integrity during psychosis with repair during remission in drug-responding schizophrenia. Int. J. Neuropsychopharmacol. 1–13.

Gebhardt, S., Hartling, F., Hanke, M., Theisen, F.M., von Georgi, R., Grant, P., Mittendorf, M., Martin, M., Fleischhaker, C., Schulz, E., Remschmidt, H., 2008. Relations between movement disorders and psychopathology under predominantly atypical antipsychotic treatment in adolescent patients with schizophrenia. Eur. Child Adolesc. Psychiatry 17, 44–53.

Gold, J.M., Egan, M.F., Kirch, D.G., Goldberg, T.E., Daniel, D.G., Bigelow, L.B., Wyatt, R.J., 1991. Tardive dyskinesia: neuropsychological, computerized tomographic, and psychiatric symptom findings. Biol. Psychiatry 30, 587–599.

Granholm, E., Bartzokis, G., Asarnow, R.F., Marder, S.R., 1993. Preliminary associations between motor procedural learning, basal ganglia T2 relaxation times, and tardive dyskinesia in schizophrenia. Psychiatry Res. 50, 33–44.

Graybiel, A.M., 1997. The basal ganglia and cognitive pattern generators. Schizophr. Bull. 23, 459–469.

Gur, R.E., Maany, V., Mozley, P.D., Swanson, C., Bilker, W., Gur, R.C., 1998. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. Am. J. Psychiatry 155, 1711–1717.

Hanson, D.R., Gottesman, I.I., 2005. Theories of schizophrenia: a genetic-inflammatory-vascular synthesis. BMC Med. Genet. 6, 7.

Harvey, I., Ron, M.A., Murray, R., Lewis, S., Barker, G., McManus, D., 1991. MRI in schizophrenia: basal ganglia and white matter T1 times. Psychol. Med. 21, 587–598.

Ho, B.C., Andreasen, N.C., 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. Arch. Gen. Psychiatry 60, 585–594.

Hof, P.R., Haroutunian, V., Friedrich, V.L., Byne, W., Buitron, C., Perl, D.P., Davis, K.L., 2003. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. Biol. Psychiatry 53, 1075–1085.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keshavan, M.S., Rosenberg, D., Sweeney, J.A., Pettegrew, J.W., 1998. Decreased caudate volume in neuroleptic-naive psychotic patients. Am. J. Psychiatry 155, 774–778.

Kubicki, M., McCarley, R., Westin, C.F., Park, H.J., Maier, S., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2007. A review of diffusion tensor imaging studies in schizophrenia. J. Psychiatr. Res. 41, 15–30.

Leh, S.E., Ptito, A., Chakravarty, M.M., Strafella, A.P., 2007. Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. Neurosci. Lett. 419, 113–118.

Lerner, V., Miodownik, C., Kaptsan, A., Bersudsky, Y., Libov, I., Sela, B.A., Witztum, E., 2007. Vitamin B6 treatment for tardive dyskinesia: a randomized, double-blind, placebo-controlled, crossover study. J. Clin. Psychiatry 68, 1648–1654.

Libov, I., Miodownik, C., Bersudsky, Y., Dwolatzky, T., Lerner, V., 2007. Efficacy of piracetam in the treatment of tardive dyskinesia in schizophrenic patients: a randomized, double-blind, placebo-controlled crossover study. J. Clin. Psychiatry 68, 1031–1037.

Lim, K.O., Helpern, J.A., 2002. Neuropsychiatric applications of DTI — a review. Neuropsychiatr. Appl. NMR Biomed. 15, 587–593.

Lin, C.C., Bai, Y.M., Chen, J.Y., Wang, Y.C., Liou, Y.J., 2008. Treatment of clozapine-associated tardive dyskinesia. Prog. Neuro-psychopharmacol. Biol. Psychiatry 32 (2), 599–600.

Liou, Y.J., Wang, Y.C., Lin, C.C., Bai, Y.M., Lai, I.C., Liao, D.L., Chen, J.Y., 2005. Association analysis of NAD(P)Hratioquinone oxidoreductase (NQO1)

Pro187Ser genetic polymorphism and tardive dyskinesia in patients with schizophrenia in Taiwan. Int. J. Neuropsychopharmacol. 8, 483–486.
Liou, Y.J., Lai, I.C., Liao, D.L., Chen, J.Y., Lin, C.C., Lin, C.Y., Chen, C.M., Bai, Y.M., Chen, T.T., Wang, Y.C., 2006a. The human dopamine receptor D2 (DRD2) gene is associated with tardive dyskinesia in patients with schizophrenia. Schizophr. Res. 86, 323–325.
Liou, Y.J., Lai, I.C., Lin, M.W., Bai, Y.M., Lin, C.C., Liao, D.L., Chen, J.Y., Lin, C.Y., Wang, Y.C., 2006b. Haplotype analysis of endothelial nitric oxide synthase (NOS3) genetic variants and tardive dyskinesia in patients with schizophrenia. Pharmacogenet. Genomics 16, 151–157.
Liou, Y.J., Wang, Y.C., Chen, J.Y., Bai, Y.M., Lin, C.C., Liao, D.L., Chen, T.T., Chen, M.L., Mo, G.H., Lai, I.C., 2007. Association analysis of polymorphisms in the N-methyl-D-aspartate (NMDA) receptor subunit 2B (GRIN2B) gene and tardive dyskinesia in schizophrenia. Psychiatry Res. 153, 271–275.
McCreadie, R.G., Thara, R., Padmavati, R., Srinivasan, T.N., Jaipurkar, S.D., 2002. Structural brain differences between never-treated patients with schizophrenia, with and without dyskinesia, and normal control subjects: a magnetic resonance imaging study. Arch. Gen. Psychiatry 59, 332–336.
McCreadie, R.G., Srinivasan, T.N., Padmavati, R., Thara, R., 2005. Extrapyramidal symptoms in unmedicated schizophrenia. J. Psychiatr. Res. 39, 261–266.
Miller, D.D., McEvoy, J.P., Davis, S.M., Caroff, S.N., Saltz, B.L., Chakos, M.H., Swartz, M.S., Keefe, R.S., Rosenheck, R.A., Stroup, T.S., Lieberman, J.A., 2005. Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. Schizophr. Res. 80, 33–43.
Minami, T., Nobuhara, K., Okugawa, G., Takase, K., Yoshida, T., Sawada, S., Ha-Kawa, S., Ikeda, K., Kinoshita, T., 2003. Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. Neuropsychobiology 47, 141–145.
Mion, C.C., Andreasen, N.C., Arndt, S., Swayze, V.W., Cohen, G.A., 1991. MRI abnormalities in tardive dyskinesia. Psychiatry Res. 40, 157–166.
Mo, G.H., Liao, D.L., Lai, I.C., Wang, Y.C., Chen, J.Y., Lin, C.Y., Chen, T.T., Chen, M.L., Bai, Y.M., Lin, C.C., Liou, Y.J., 2007. Support for an association of the C939T polymorphism in the human DRD2 gene with tardive dyskinesia in schizophrenia. Schizophr. Res. 97, 302–304.
Munetz, M.R., Benjamin, S., 1988. How to examine patients using the Abnormal Involuntary Movement Scale. Hosp. Community Psychiatr. 39, 1172–1177.
Okugawa, G., Nobuhara, K., Minami, T., Tamagaki, C., Takase, K., Sugimoto, T., Sawada, S., Kinoshita, T., 2004. Subtle disruption of the middle cerebellar peduncles in patients with schizophrenia. Neuropsychobiology 50, 119–123.
Okugawa, G., Nobuhara, K., Sugimoto, T., Kinoshita, T., 2005. Diffusion tensor imaging study of the middle cerebellar peduncles in patients with schizophrenia. Cerebellum 4, 123–127.
Okugawa, G., Nobuhara, K., Minami, T., Takase, K., Sugimoto, T., Saito, Y., Yoshimura, M., Kinoshita, T., 2006. Neural disorganization in the superior cerebellar peduncle and cognitive abnormality in patients with schizophrenia: a diffusion tensor imaging study. Prog. Neuro-psychopharmacol. Biol. Psychiatry 30, 1408–1412.
Pantelis, C., Stuart, G.W., Nelson, H.E., Robbins, T.W., Barnes, T.R., 2001. Spatial working memory deficits in schizophrenia: relationship with tardive dyskinesia and negative symptoms. Am. J. Psychiatry 158, 1276–1285.
Schooler, N.R., Kane, J.M., 1982. Research diagnoses for tardive dyskinesia. Arch. Gen. Psychiatry 39, 486–487.
Schultz, W., Tremblay, L., Hollerman, J.R., 2000. Reward processing in primate orbitofrontal cortex and basal ganglia. Cereb. Cortex 10, 272–284.
Shihabuddin, L., Buchsbaum, M.S., Hazlett, E.A., Haznedar, M.M., Harvey, P.D., Newman, A., Schnur, D.B., Spiegel-Cohen, J., Wei, T., Machac, J., Knesaurek, K., Vallabhajosula, S., Biren, M.A., Ciaravolo, T.M., Luu-Hsia, C., 1998. Dorsal striatal size, shape, and metabolic rate in never-medicated and previously medicated schizophrenics performing a verbal learning task. Arch. Gen. Psychiatry 55, 235–243.
Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr. Scand., Suppl. 212, 11–19.
Stephan, K.E., Baldeweg, T., Friston, K.J., 2006. Synaptic plasticity and dysconnection in schizophrenia. Biol. Psychiatry 59, 929–939.
Szeszko, P.R., Ardekani, B.A., Ashtari, M., Kumra, S., Robinson, D.G., Sevy, S., Gunduz-Bruce, H., Malhotra, A.K., Kane, J.M., Bilder, R.M., Lim, K.O., 2005. White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study. Am. J. Psychiatry 162, 602–605.
Szymanski, S., Gur, R.C., Gallacher, F., Mozley, L.H., Gur, R.E., 1996. Vulnerability to tardive dyskinesia development in schizophrenia: an FDG-PET study of cerebral metabolism. Neuropsychopharmacology 15, 567–575.
Takase, K., Tamagaki, C., Okugawa, G., Nobuhara, K., Minami, T., Sugimoto, T., Sawada, S., Kinoshita, T., 2004. Reduced white matter volume of the caudate nucleus in patients with schizophrenia. Neuropsychobiology 50, 296–300.
Tenback, D.E., van Harten, P.N., Slooff, C.J., van Os, J., 2006. Evidence that early extrapyramidal symptoms predict later tardive dyskinesia: a prospective analysis of 10, 000 patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) study. Am. J. Psychiatry 163, 1438–1440.
Tenback, D.E., van Harten, P.N., Slooff, C.J., van Os, J., 2007. Worsening of psychosis in schizophrenia is longitudinally associated with tardive dyskinesia in the European Schizophrenia Outpatient Health Outcomes study. Compr. Psychiatry 48, 436–440.
Ueyama, K., Fukuzako, H., Takeuchi, K., Hirakawa, K., Fukuzako, T., Hokazono, Y., Takigawa, M., Matsumoto, K., 1993. Brain atrophy and intellectual impairment in tardive dyskinesia. Jpn. J. Psychiatry Neurol. 47, 99–104.
Uranova, N.A., Vostrikov, V.M., Orlovskaya, D.D., Rachmanova, V.I., 2004. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr. Res. 67, 269–275.
Volkow, N.D., Wolf, A.P., Brodie, J.D., Cancro, R., Overall, J.E., Rhoades, H., Van Gelder, P., 1988. Brain interactions in chronic schizophrenics under resting and activation conditions. Schizophr. Res. 1, 47–53.
Waddington, J.L., O'Callaghan, E., Buckley, P., Madigan, C., Redmond, O., Stack, J.P., Kinsella, A., Larkin, C., Ennis, J.T., 1995. Tardive dyskinesia in schizophrenia. Relationship to minor physical anomalies, frontal lobe dysfunction and cerebral structure on magnetic resonance imaging. Br. J. Psychiatry 167, 41–44.
Winterer, G., Weinberger, D.R., 2004. Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. Trends Neurosci. 27, 683–690.
Wonodi, I., Hong, L.E., Thaker, G.K., 2005. Psychopathological and cognitive correlates of tardive dyskinesia in patients treated with neuroleptics. Adv. Neurol. 96, 336–349.
Zhang, X.Y., Tan, Y.L., Zhou, D.F., Cao, L.Y., Wu, G.Y., Haile, C.N., Kosten, T.A., Kosten, T.R., 2007. Disrupted antioxidant enzyme activity and elevated lipid peroxidation products in schizophrenic patients with tardive dyskinesia. J. Clin. Psychiatry 68, 754–760.