Altered white matter tract integrity in drug-naïve and chronic schizophrenia patients: a study using automatic tract-specific analysis of the whole brain

Chen-Hao Wu[1,2], Yu-Jen Chen[2], Yun-Chin Hsu[2], Yu-Chun Lo[2], Tzung-Jeng Hwang[3], Hai-Gwo Hwu[3], Chung-Ming Chen[1], and Wen-Yih Isaac Tseng[1,2]

[1]*Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan, Taiwan,* [2]*Center for Optoelectronic Medicine, National Taiwan University College of Medicine, Taipei, Taiwan,* [3]*Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan*

Introduction The study of schizophrenia patients at chronic stage cannot address questions about the timing of the observed white matter changes [1]. Chronic patients have been exposed for long periods to various confounders, such as antipsychotic medication, medical comorbidity, and potentially exaggerated aging effects [2]. Therefore, examination of white matter abnormalities closer to illness onset is important in the effort to disentangle the primary white matter pathology of schizophrenia from secondary changes that may occur over time. In order to address these issues and determine whether the white matter abnormalities of chronic schizophrenia are present at illness onset, we conducted a diffusion spectrum imaging (DSI) investigation in three groups of drug-naïve, chronic schizophrenia patients and healthy controls for comparison.

Materials and Methods Participants recruited in the study included 36 chronic schizophrenia patients (15 male, 20 female; mean age 30.0 years), 25 drug-naïve schizophrenia patients (15 males, 10 female; mean age 26.5 years), and 34 healthy control participants (17 male, 17 female; mean age 28.9 years). DSI was performed on a 3T magnetic resonance imaging system (TIM Trio, Siemens) using a twice-refocused balanced echo diffusion echo planar imaging (EPI) sequence, TR/TE = 9600/130 ms, image matrix size = 80 x 80, and slice thickness = 2.5 mm. The white matter tract integrity was assessed using a novel automatic tract-specific analysis (TBAA) [3]. Specifically, the whole brain 74 white matter tracts were reconstructed on the NTU-DSI-122 template using deterministic tractography. A transformation map was established between the NTU-DSI-122 template and the individual's DSI data. The tracts' coordinates in the template space were transformed to the native space of the individual's DSI data. Finally, the generalized fractional anisotropy (GFA) values of the 74 tracts were sampled from the individual's DSI data. To compare the mean GFA values among the three groups, we used analyses of covariance (ANCOVAs) with Benjamini-Hochberg corrections for multiple comparisons. Age was used as covariates to minimize their effects on the study variables. To determine the differences between the groups, post-hoc Scheffe tests were applied. To study the associations between the tracts determined by the ANCOVAs, partial correlation analyses were performed between the chronic patients' mean GFA values and their duration of illness while controlling for age.

Results There was no significant difference between the groups with respect to age, gender, and handedness. Table I summarizes the seven tracts showing significant differences ($p \leq 0.05$) between groups in ANCOVA, followed by the Benjamini-Hochberg correction for multiple comparisons. In post-hoc Scheffe analysis, chronic schizophrenia patients showed significantly lower GFA values than healthy controls in the seven tracts ($p \leq 0.05$), and the drug-naïve patients showed lower GFA in these tracts except for the corpus callosum to the bilateral dorsolateral prefrontal cortices (DLPFC) ($p = 0.153$). The partial correlations with duration of illness were significant in the corpus callosum to the bilateral DLPFC ($r = -0.379$, $p = 0.027$) and the bilateral hippocampi ($r = -0.412$, $p = 0.015$) but failed to reach statistical significance in the other five tracts. (Table II).

Discussion White matter integrity of the CC to DLPFC was not significantly reduced in illness onset, but significantly reduced in the chronic stage, suggesting a secondary change. The corpus callosum to bilateral hippocampi was impaired in illness onset and even worse in the chronic stage, indicating combination of primary pathology and secondary changes. The alterations of the other five tracts were present in illness onset and tended to persist throughout disease course, suggesting potential trait markers.

References [1] Friedman, J.I., et al. (2008) Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. American Journal of Psychiatry [2] Bartzokis, G., et al. (2003) Dysregulated brain development in adult men with schizophrenia: a magnetic resonance imaging study. Biological Psychiatry [3] Wu, C.H., et al. (2014) Altered integrity of the right arcuate fasciculus as a trait marker of schizophrenia: A sibling study using tractography-based analysis of the whole brain. Human Brain Mapping

Table I Comparisons of the mean GFA values of the white matter tracts of the three groups

	Chronic patients	Drug-naive patients	Healthy controls	ANCOVA	Post-hoc Scheffe: Chronic *vs.* Controls	Post-hoc Scheffe: Drug-naive *vs.* Controls	Post-hoc Scheffe: Chronic *vs.* Drug-naive
Fiber tract	GFA value Mean ± SD	GFA value Mean ± SD	GFA value Mean ± SD	*P*-value	*P*-value	*P*-value	*P*-value
Rt. AF	0.264 ± 0.017	0.265 ± 0.020	0.278 ± 0.012	0.042*	0.004*	0.014*	0.991
Lt. FX	0.147 ± 0.025	0.152 ± 0.021	0.177 ± 0.015	0.003*	<0.001*	<0.001*	0.611
Rt. FX	0.195 ± 0.022	0.196 ± 0.019	0.218 ± 0.014	0.003*	<0.001*	<0.001*	0.950
Lt. OR	0.312 ± 0.016	0.309 ± 0.036	0.330 ± 0.013	0.042*	0.004*	0.009*	0.836
CC to DLPFC	0.325 ± 0.020	0.328 ± 0.024	0.338 ± 0.014	0.042*	0.033*	0.153	0.900
CC to TP	0.189 ± 0.020	0.186 ± 0.024	0.205 ± 0.013	0.018*	0.002*	0.004*	0.822
CC to HP	0.181 ± 0.028	0.178 ± 0.026	0.202 ± 0.021	0.018*	0.003*	0.004*	0.931

Note. *Statistically significant. Abbreviations: Rt., right; Lt., left; AF, arcuate fasciculus; FX, fornix; OR, optic radiation; CC, corpus callosum; DLPFC, dorsolateral prefrontal cortex; TP, temporal pole; HP, hippocampus;

Table II Partial correlation with duration of illness

Fiber tract	*r*	*P*-value
Rt. AF	-0.108	0.542
Lt. FX	-0.192	0.276
Rt. FX	-0.219	0.213
Lt. OR	-0.204	0.247
CC to DLPFC	-0.379	0.027*
CC to TP	-0.319	0.066
CC to HP	-0.412	0.015*

Note. *Statistically significant