# Altered white matter tract integrity as a potential endophenotype of schizophrenia: a sibling study using automatic tract-specific analysis of the whole brain

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***Introduction*** Alteration of white matter tract integrity was reported in siblings of schizophrenia patients in several studies using voxel-based analysis (VBA) [1]. Some studies suggested that tract-specific analysis (TSA) may be more specific and reliable than VBA [2]. However, manual tractography, which is currently the main-stream approach, is time consuming and not feasible for analyzing whole brain tracts. In this study, we proposed a new method to perform tract-specific analysis over the whole brain, named tract-based automatic analysis (TBAA), using a diffusion spectrum imaging (DSI) template and a tract atlas. Using this method, we assessed the entire brain white matter tracts and searched for potential white matter tracts which could represent a possible endophenotype of schizophrenia. We hypothesized that the potential endophenotype of white matter tracts showed altered integrity in both patients and siblings, and the alteration had a gradation of differences from patients, siblings to contols.

***Materials and Methods*** Participants recruited in the study included 31 individuals with DSM-IV diagnosed schizophrenia (17 male, 14 female; mean age 33.8 years), 31 siblings of individuals with schizophrenia (19 males, 12 female; mean age 33.5 years), and 31 healthy control participants (16 male, 15 female; mean age 31.0 years). The TBAA method requires two important pieces of information, a high quality DSI template and a whole brain WM tract atlas. The DSI template was constructed by coregistering 122 healthy participants' DSI datasets (Male: Female = 63:59) in the Montreal Neurobiology Institute (MNI) space using a coregistration method under the frame work of Large Deformation Diffeomorphic Metric Mapping (LDDMM) [3]. Whole brain WM tracts were reconstructed on the DSI template by an expert using multiple regions of interest (ROIs) and whole brain seeding [4]. A total of 117 tracts were reconstructed from 60 ROIs defined in the Automatic Anatomical Labeling system. Each reconstructed tract was subdivided into multiple steps with even spacing [5] and the step coordinates along tract bundles were saved as sampling coordinates. The procedures of TBAA method were as follow. 1) Study subjects were coregistered to create a study specific template (SST) using LDDMM. 2) The SST was coregistered to the DSI template. 3) Sampling coordinates were transformed from the DSI template to individual DSI datasets via the transformation matrix between DSI template and SST as well as the matrix between SST and individual DSI. 4) The generalized fractional anisotropy (GFA) values were sampled in the native space using the transformed sampling coordinates and a 2D array of GFA profiles was created for each subject. To compare GFA values of each tract among three groups, we used one-way analysis of variance (ANOVA); Benjamini-Hochberg procedure was used to correct for multiple comparisons. A trend analysis, the Jonckheere–Terpstra (J–T) test and Kendall's tau rank correlation, was performed to examine whether the data of each group was significantly ordered. Comparison between study groups was followed by Tukey HSD post-hoc tests.

***Results*** There were no significant differences between the groups with respect to age, gender, education, and handedness. Table 1 summarizes the fifteen tracts showing significant differences between groups in ANOVA, followed by the Benjamini-Hochberg correction for multiple comparisons. The J–T test for the fifteen tracts showed intermediate values in siblings, indicating a trend toward distinguishing the patient group from healthy control subjects. Post-hoc Tukey HSD analysis revealed, compared with healthy controls, both siblings and patients yielded a significant decrease in the GFA values of the right arcuate fascuculus and a significant increase in a tract connecting left thalamus and precentral gyrus (Fig1).

***Discussion*** Using TBAA method, we found significantly ordered white matter alterations in the right arcuate fascuculus and the tract between left thalamus and precentral gyrus. These two tracts could become a potential endophenotype, and might be helpful for the diagnosis of schizophrenia as well as for early identification of clinically healthy subjects who are at risk of disease.

***References*** [1] Hoptman, M.J. et al. (2008). A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. Schizophrenia research. [2] Kanaan, R.A. et al. (2006). Tract-specific anisotropy measurements in diffusion tensor imaging. Psychiatry research.[3] Hsu, Y. C. et al. (2012). A large deformation diffeomorphic metric mapping solution for diffusion spectrum imaging datasets. Neuroimage. [4] Lo, Y. C. et al. (2011). The loss of asymmetry and reduced interhemispheric connectivity in adolescents with autism: a study using diffusion spectrum imaging tractography. Psychiatry Res. [5] Chiang, W. Y. et al. (2007). Tract-Specific Analysis of Human White Matter: Mean-path Based Method. Proc 16th ISMAR.

Table 1
Post hoc test results following a significant ANOVA test

| | | | | | | | Post hoc Tukey HSD | |
|---|---|---|---|---|---|---|---|---|
| | | | | Kendall's tau rank | Jonckheere Terpstra | Patients vs controls | Siblings vs controls | Patients vs siblings |
| *Tracts* | Controls Mean GFA | Siblings Mean GFA | Patients Mean GFA | correlation | Trend Test | *P-value* | *P-value* | *P-value* |
| Right arcuate fasciculus | 0.286 | 0.274 | 0.269 | -0.235 | 0.004[a] | 0.004* | [b]0.048* | 0.604 |
| Left fornix | 0.176 | 0.169 | 0.152 | -0.415 | 0.000[a] | 0.000* | 0.255 | 0.000* |
| Right fornix | 0.159 | 0.155 | 0.138 | -0.381 | 0.000[a] | 0.000* | 0.632 | 0.000* |
| Left inferior longitudinal fasciculus | 0.355 | 0.352 | 0.338 | -0.249 | 0.002[a] | 0.006* | 0.858 | 0.026* |
| Right superior longitudinal fasciculus I | 0.279 | 0.270 | 0.261 | -0.258 | 0.001[a] | 0.003* | 0.230 | 0.220 |
| Right putamen to opercular part of inferior frontal gyrus | 0.274 | 0.270 | 0.259 | -0.261 | 0.001[a] | 0.001* | 0.899 | 0.015* |
| Left putamen to triangular part of inferior frontal gyrus | 0.264 | 0.263 | 0.253 | -0.226 | 0.005[a] | 0.006* | 0.888 | 0.022* |
| Left thalamus to medial part of superior frontal gyrus | 0.242 | 0.241 | 0.232 | -0.261 | 0.001[a] | 0.004* | 0.986 | 0.008* |
| Left thalamus to precentral gyrus | 0.262 | 0.268 | 0.270 | 0.255 | 0.002[a] | 0.002* | [b]0.041* | 0.543 |
| Right thalamus to precentral gyrus | 0.260 | 0.263 | 0.270 | 0.274 | 0.001[a] | 0.001* | 0.451 | 0.031* |
| Corpus callosum to middle frontal gyrus | 0.284 | 0.263 | 0.270 | -0.208 | 0.010[a] | 0.021* | 0.985 | 0.010* |
| Corpus callosum to medial part of superior frontal gyrus | 0.325 | 0.324 | 0.309 | -0.254 | 0.002[a] | 0.005* | 0.922 | 0.015* |
| Corpus callosum to superior frontal gyrus | 0.309 | 0.304 | 0.291 | -0.277 | 0.001[a] | 0.002* | 0.594 | 0.040* |
| *Genu of the corpus callosum* | 0.318 | 0.311 | 0.299 | -0.247 | 0.002[a] | 0.003* | 0.470 | 0.072 |
| *Corpus callosum to temporal pole* | 0.235 | 0.230 | 0.209 | -0.361 | 0.000[a] | 0.000* | 0.512 | 0.000* |

Note. [a]The mean GFA of the siblings was significantly intermediate between the patients and the normal controls with the Jonckheere–Terpstra test.

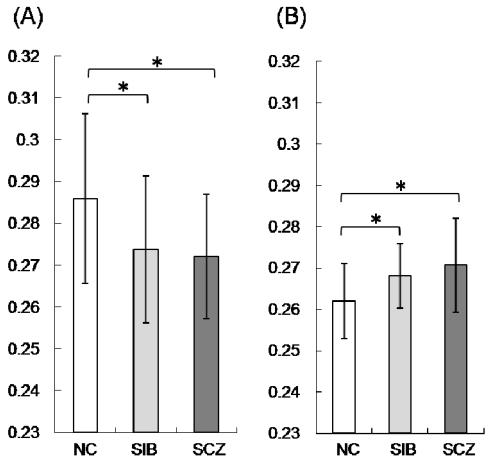


Figure1. Group differences in GFA values of the right arcuate fasciculus (A) and the tract between left thalamus and precentral gyrus (B). Values are reported as mean ± standard deviation. NC, normal control subjects; SIB, siblings; SCZ, schizophrenic subjects; *$p < .05$