

White matter abnormalities in schizophrenia: A diffusion spectrum imaging study using whole brain tract-specific analysis

Yu-Jen Chen¹, Chun-Chieh Fan², Yung-Chin Hsu¹, Yu-Chun Lo¹, Chih-Ming Liu³, and Wen-Yih Isaac Tseng¹

¹Center for Optoelectronic Medicine, National Taiwan University College of Medicine, Taipei, Taipei, Taiwan, ²Department of Cognitive Science, UC San Diego, CA, United States, ³Department of Psychiatry, National Taiwan University Hospital, Taipei, Taipei, Taiwan

Purpose Schizophrenia is considered to have abnormalities in white matter that affect brain connectivity. It is not clear whether these abnormalities affect the entire white matter, or if they are localized and limited to specific white matter tracts. To characterize the abnormalities of white matter tracts over the whole brain, however, traditional tractography method is too time-consuming to reconstruct all the fiber tracts for each subject. In this study, we proposed a high throughput tract-specific analysis, called tract-based automatic analysis (TBAA), to investigate the abnormalities of white matter tracts in schizophrenia using diffusion spectrum imaging (DSI). Threshold-free cluster enhancement (TFCE) [1] was performed to exploit spatially extended signals of each tract. A permutation test for controlling family-wise error rate (FWER) [2] was performed to estimate the false discoveries from the whole brain analysis.

Methods Fifty-four patients with schizophrenia and 54 healthy controls matched on age (patients: 34.4 ± 8.6 , range: 19-52; controls: 32.3 ± 9.0 , range: 19-49) and gender (patients: 29males, 25 females; control: 28 males, 26 females) were recruited for the analysis. Images were acquired on a 3T MRI system with a 32-channel phased array head coil (Tim Trio, Siemens, Erlangen, Germany). DSI was performed using a twice-refocused balanced echo diffusion echo planar imaging (EPI) sequence, TR/TE = 9600/130 ms, image matrix size = 80×80 , spatial resolution = $2.5 \times 2.5 \text{ mm}^2$, and slice thickness = 2.5 mm. 102 diffusion encoding gradients with the maximum diffusion sensitivity $b_{\max} = 4000 \text{ s/mm}^2$ were sampled on the grid points in a half sphere of the 3D q-space with $|q| \leq 3.6$ units [3]. For tract-specific analysis, TBAA was applied with a high quality DSI template and pre-segmented white matter tracts over the whole brain [4]. The DSI template was constructed by coregistering 122 healthy participants' DSI datasets using the Large Deformation Diffeomorphic Metric Mapping (LDDMM) method [5], and whole brain white matter tracts were reconstructed on the template by an expert using multiple regions of interest defined in the Automatic Anatomical Labeling system. Each reconstructed tract was subdivided into 100 steps with even spacing and the step coordinates along tracts were saved as sampling coordinates. The procedures of TBAA method were as follow. 1) A study specific template (SST) was created via coregistering all participants' DSI datasets using LDDMM. 2) The SST was coregistered to the DSI template. 3) Sampling coordinates of the tracts were transformed from the DSI template to individual DSI datasets via the transformation matrix between DSI template and SST as well as the transformation between SST and individual DSI. 4) Generalized fractional anisotropy (GFA) values were sampled in the native DSI space using the transformed sampling coordinates, resulting in a 2D array (117 tracts \times 100 steps) of GFA profiles for each subject. Stepwise comparisons between two groups were performed by applying TFCE ($TFCE(p) = \int_{h=h_0}^{h_p} e(h)^E h^H dh$, where h_p is the statistical t value at step p ; e is the cluster extent which survives at a given threshold h ; E and H are assigned weights to the cluster extent and the statistical magnitude) with $E=2$ and $H=2$. A permutation test was performed to estimate the FWER adjusted p values for multiple comparisons.

Results We found 95 clusters spanning across 66 tracts showing significant differences (FWER adjusted $p < 0.05$) between schizophrenia group and control group. As the figure 1 showed, among the 66 tracts, there were 42 tracts showing clusters with significantly higher GFA values in control group than in schizophrenia group (red color), 17 tracts showing clusters with significantly lower GFA values in control group than in schizophrenia group (green color), and 7 tracts containing clusters with both significantly higher and lower GFA values between control group and schizophrenia group (blue color). In the association fibers, the significant tracts were bilateral fornix, bilateral superior longitudinal fasciculus, bilateral uncinate fasciculus, right inferior frontal-occipital fasciculus, right arcuate fasciculus, and left inferior longitudinal fasciculus. In the callosal fibers, four portions of corpus callosum were identified, including fibers connecting bilateral cuneus, bilateral precuneus, bilateral frontal lobes, and bilateral temporal pole. Moreover, bilateral sensory tracts, bilateral frontal-striatal tracts and bilateral thalamo-cortical tracts also showed significant differences.

Discussion In this study, we employed a high throughput tract-specific analysis and a feasible statistical testing to examine multiple fiber tracts in schizophrenia patients and healthy controls. Our results showed consistent findings in association fibers and callosal fibers with previous studies [6]. Furthermore, we also found many significant differences in projection fibers, such as frontal-striatal tracts and thalamo-cortical tracts, which were seldom reported in previous literatures. Moreover, based on the step-wise comparisons, clusters with significant difference could be discovered after applying TFCE and controlling FWER. These significant clusters may provide advanced information more specific than mean GFA of the entire fiber tracts.

References [1] Nichols, T. et al. Stat Methods Med Res (2003). [2] Smith, S. M. et al. NeuroImage (2009). [3] Wedeen, V.J. et al. Magn Reson Med. (2005). [4] Lo, Y.C. et al. Proc ISMRM (2013). [5] Hsu, Y.C. et al. Neuroimage (2012). [6] Boos, H.B.M. et al. European Neuropsychopharmacology (2013).

Figure 1. The significantly different tracts between schizophrenia patients and healthy controls in (a) association fibers, (b) callosal fibers, and (c) projection fibers. Red showed tracts with higher GFA values in controls than in patients. Green showed tracts with higher GFA values in patients than in controls. Blue showed the tracts with mixed conditions between controls and patients.

