

# A diffusion spectrum tractography study on fiber integrity of fornix and correlation with clinical symptoms in schizophrenia

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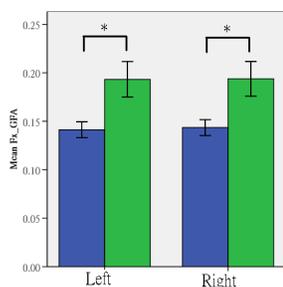
**Introduction** The fornix is a white matter fiber tract in the limbic system interconnecting the hippocampus and mammillary body, and has been long thought to be involved in schizophrenia [1]. However, the fornix has been less thoroughly investigated in the pathophysiology of this mental illness. In post-mortem studies, it has been reported that left hemisphere hippocampus volume reduction was not only more prominent in patients with schizophrenia [2], but increased fiber density due to less myelination in the left fornix has also been implicated in male patients [3]. Using diffusion tensor imaging (DTI), Fitzsimmons [4] reported that there is a bilateral fractional anisotropy (FA) decrease in schizophrenia patients, compared with control subjects. Luck's team [5] also found significant overall FA reductions in the fornix in first episode schizophrenia (FES) patients relative to controls. However, they did not find any associations between FA values and the total clinical scores of positive and negative symptoms scale (PANSS). To better understand the relationship between the anatomical changes and clinical syndromes, we used diffusion spectrum imaging (DSI) to compare the general fractional anisotropy (GFA) of the fornix between patients and controls, and we also explored the correlations between GFA values and subscores of PANSS.

**Materials and Methods** We recruited 20 patients with chronic schizophrenia (M:F = 10:10) who were diagnosed according to DSM-IV criteria and 20 age- and gender-matched healthy controls. Nineteen of the patients' PANSS scores were measured by clinical psychiatrists. Our DSI images were acquired using a twice-refocused balanced echo diffusion echo planar imaging sequence covering the whole brain on a 3T MRI system with a 32-channel head coil (Siemens, Erlangen, Germany). The following scan criteria were used: TR/TE = 9600/130 ms, image matrix size = 80 x 80, spatial resolution = 2.5 x 2.5 mm<sup>2</sup>, and slice thickness = 2.5 mm. The diffusion weighting value (b-value) was set from 0 to maximum 4000 s/mm<sup>2</sup> along 102 diffusion encoding gradient directions. The diffusion probability density function P(r) was obtained from the echo signal S(q) by Fourier transform. And the orientation distribution function (ODF) was calculated by taking the second moment of P(r) along each radial direction. Next, the intravoxel primary fiber orientations which were determined by decomposing the original ODF into several partial ODFs were used for tractography reconstruction. Generalized fractional anisotropy (GFA) of each voxel was quantified according to the shape of the original ODF. Later, tractography was reconstructed using a streamline-based algorithm adapted for DSI data by our in-house software DSI studio and the targeted tracts (fornix) were depicted by specific regions-of-interest (ROIs). Finally, the GFA was projected onto a single mean path of a specific tract by mean path analysis. We compared the GFA on each side of the fornix between patients and controls, and we subsequently performed Pearson's correlation analysis of the patients' GFA and their severity subscores of PANSS.

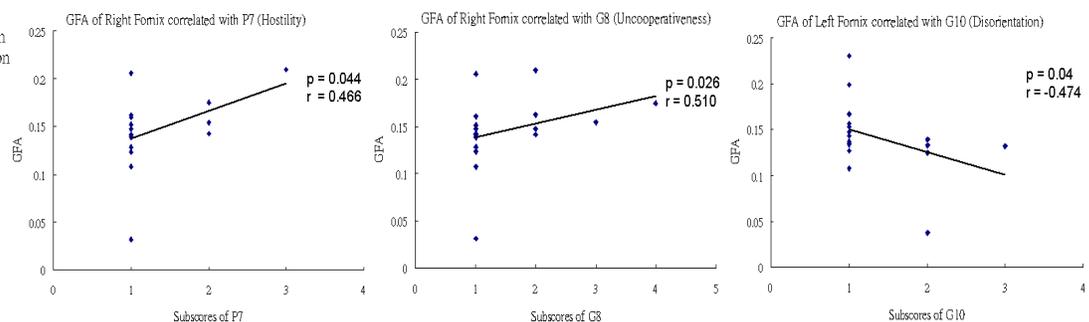
**Results** There was a significant reduction of GFA in bilateral fornix in schizophrenia patients as compared to the controls, and the asymmetry in both groups was not significant [Fig. 1]. Moreover, we found positive correlations between GFA values of right fornix and the PANSS subscore P7 (Hostility; r = 0.466, p = 0.044), G8 (Uncooperativeness; r = 0.510, p = 0.026) as well as a negative correlation between the left fornix and the subscore G10 (Disorientation; r = -0.474, p = 0.040) [Fig. 2].

**Discussion** The finding of reduced GFA in bilateral fornix in schizophrenia is consistent with the previous studies using DTI [4-5]. The function of fornix was conventionally thought relating to memory [6], emotion [7] and empathy [8]. However, we found associations of the fornix with different subscores in PANSS. The negative correlation between GFA values of left fornix and the subscore G10 (Disorientation) implies that reduced GFA in the left fornix might associate with greater severity of conceptual organization. On the other hand, the positive correlation between GFA values of right fornix and the subscores P7 (Hostility) and G8 (Uncooperativeness) suggests that increased GFA in the right fornix might be related to greater severity of hostility and uncooperativeness. Our findings demonstrate the usefulness of DSI tractography to investigate the functional relevance of the white matter tracts in schizophrenia, thus extending our understanding of the disease pathophysiology. Further studies are required to examine the gender effects on the GFA asymmetry and on the correlation with the severity of clinical symptoms.

**References** [1] E.F. Torrey, Schizophr Res. 2007 Dec;97(1-3):215-25. [2] M.E. Shenton, et al., Schizophr Res. 49, 1-52. [3] S.A. Chance, et al., Am. J. Psychiatry 156, 1720-1724. [4] J. Fitzsimmons, et al., Schizophr Res. 2009 39-46. [5] D. Luck, et al., Schizophr Res. 2010 61-63. [6] S.D. Van, HIPPOCAMPUS. 2010. [7] L. Concha, et al., AJNR Am J Neuroradiol 26:2267-2274, October 2005. [8] K. Schnell, et al., NeuroImage, 2010.



**Figure 1** There is a significant bilateral reduction of GFA in the fornix in schizophrenia patients (Sch) compared to the controls (Con).



**Figure 2** GFA of right fornix is positive related to P7 and G8 (left and middle). GFA of left fornix is negative related to G10 (right).