White Matter Abnormalities in Tardive Dyskinia: A Diffusion Tensor Image Study

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Introduction

Tardive dyskinesia (TD), the most severe side-effect of antipsychotics, is characterized by late-onset, repetitive involuntary choreiform movement, tics and grimaces of the orofacial muscles, as well as dyskinesia of the distal limbs, paraspinal muscles, and diaphragm. Pervious studies have suggested that schizophrenic patients with TD had an excess of neurodevelopmental disturbance, particularly minor physical anomalies, in association with cognitive dysfunction and abnormalities of cerebral structure [1-2]. Diffusion tensor imaging (DTI), a useful tool to examine and quantify the microstructure of white matter, has a great potential for studying of WM abnormalities in neuropsychiatric disorders [3-4]. Recently, a growing number of studies have suggested that disturbances in the connectivity between different brain regions might be responsible for the clinical symptoms and cognitive dysfunctions observed in schizophrenia [5]. However, schizophrenia with/without TD has never been compared and discussed with healthy subjects based on this new technique. Here we presented a detailed study with side-by-side comparisons in schizophrenia subjects with and without TD and healthy subjects applying the high resolution voxel-based DTI technique.

Methods

18 Schizophrenia patients with TD (mean age is 43.06±11.23 y/o, 13 female and 5 male) and 18 Schizophrenia patients without TD (mean age is 41.36±9.64 y/o, 12 female and 6 male) , and 36 healthy subjects (mean age is 42.73±1.1 y/o, 23 female and 13 male), who were confirmed by MINI international neuropsychiatric interview were recruited. These three groups were matched in age, gender, and handedness. All MR scans were performed on a 1.5T MR system (Excite II; GE Medical Systems, Milwaukee, Wis., USA) at the Veterans General Hospital Taipei. Whole brain diffusion-weighted images were acquired using single shot diffusion spin-echo EPI sequence with TR/TE = 17000/68.9 ms, voxel size = 2 x 2 x 2.2 mm3, b = 900 s/mm², 13 directions, and NEX = 6. T1-weighted structural images were also acquired with TR/TE= 8.54/1.84ms, voxel size=1*1*1.5 mm^3. Time for each scan was 30 minutes. Fractional anisotropy (FA) values were calculated by an in-house program. Subsequent voxelwise analysis including FA image registration and normalization were performed on SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). For image analysis, non-diffusion-weighted images of each participant were preliminary coregistered to T1 images which were then normalized to a customized T1 template. Before smoothed with an isotropic 8mm^3 Gaussian kernel, FA maps were coregistered and normalized applying the deformation parameters generated in former step. A voxel-based one-way analysis of variance (ANOVA) was performed to investigate the differences in FA values among three groups. In the *post-hoc* tests, statistical criteria were set at $P<0.01$ and cluster size larger than 50 voxels at the same time.

Results

Schizophrenia patients without TD showed significantly lower FA in brain stem, corpus callosum, frontal sub-gyral white matter (WM) and middle temporal WM compared to normal controls (Fig 1). Patient with TD demonstrated significantly widespread FA decrease over cerebellum WM, brain stem, frontal lobe WM, temporal lobe WM, corpus callosum, parietal lobe WM, anterior cingulated WM, internal capsule and external capsule compared with normal control (Fig 2). Side-by-side comparisons of schizophrenia patients with TD to those without TD, schizophrenia patients with TD showed significantly lower FA in external capsule, temporal lobe WM, frontal lobe WM, parietal lobe WM, cingulated WM and corpus callosum (Fig 3).

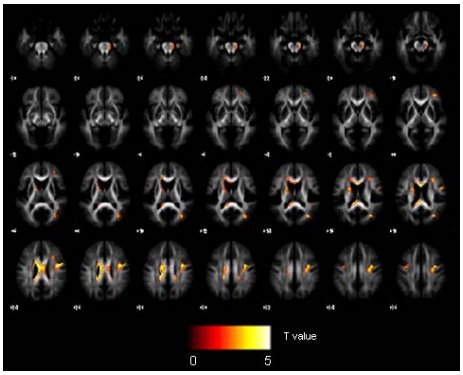

Figure 1: Comparing to normal controls, a smaller FA was observed in schizophrenia patients without TD.

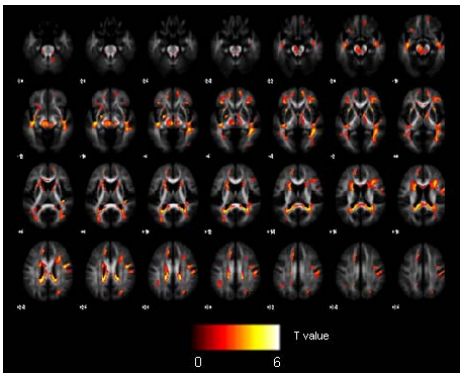

Figure 2: FA also decreased in schizophrenia patients with TD when comparing to normal controls.

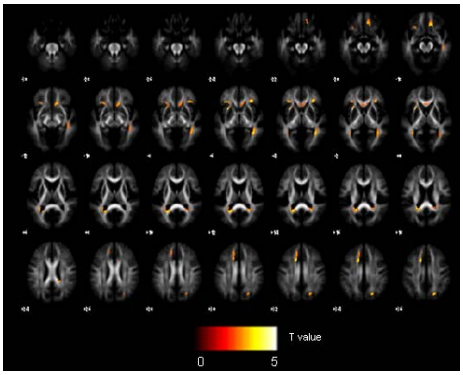

Figure 3: FA decreased more in schizophrenia patients with TD than those without TD.

Conclusions

Our findings suggested that schizophrenia patients with TD had more widespread WM deficiency over the whole brain than either those without TD or normal controls, especially severe in external capsule, corpus callosum, frontal WM and optic radiation. Deficiency in external capsule could explain why the TD patients would have repetitive involuntary choreiform movement, tics, grimaces of the orofacial muscles and other abnormality movement symptoms. Moreover, FA deficits founded in frontal lobe WM, corpus callosum and optic radiation might be highly relate to the poor performances in cognitive function tests and visual attention deficits of patients with TD. Based on these preliminary results, we are able to clearly classify the different abnormal brain areas between schizophrenia patients with/without TD and normal controls. In order to understand the relationships of schizophrenia with/without TD further, subsequent studies are focused in the correlations of clinical symptoms, behavioral representations and brain WM integrity abnormalities.

Acknowledgements

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References

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