A Diffusion tensor MRI study of White Matter microstructure in Tardive Dyskinia: Relation to Symptoms

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Introduction

Tardive dyskinesia (TD) 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]. Recently, increasing evidence suggests that a disturbance in connections between different brain regions, rather than abnormalities within the separate regions themselves, is responsible for the clinical symptoms and cognitive dysfunctions observed in schizophrenia [3]. In this research, voxel-wised DTI analysis was performed to investigate the differences among schizophrenia with/without TD and healthy controls. Relationship between clinical symptom and WM microstructure abnormality were also examined.

Methods

20 schizophrenia patients with TD (41.5±10.1 y/o, 15 female/5 male), 20 schizophrenia patients without TD (40.5±9.3 y/o, 15 female/5 male) and 20 healthy subjects (41.2±10.1 y/o, 15 female/5 male), who were confirmed by MINI international neuropsychiatric interview, were recruited. These three groups were matched in age, gender, and handedness. Patient groups underwent the following clinical rating: Positive and Negative Syndrome Scale (PANSS) scores, the Abnormal Involuntary Movement Scale (AIMS) ratings, and Simpson-Angus Scale (SAS). 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. All image processing were performed on the SPM2 (Wellcome Department of Imaging Neuroscience, London, UK) and the detail processing procedure of voxel-wised FA analysis was the same as our previous article [4]. One-way analysis of variance (ANOVA) was performed to investigate the differences in FA values among three groups. In order to remove potential confounds (duration of illness, dosage of medication, and age of onset) in disease groups, the analysis of covariance (ANCOVA) was performed to investigate the FA differences between schizophrenia with/without TD groups. An uncorrected P-value < 0.005 as well as a cluster size more than 50 contiguous voxels was set to putatively detect the significant between-groups differences. To further elucidate the white matter microstructure abnormality correlates of symptom severity, correlation analyses were performed in disease-combined groups to correlate the symptom severity scores with the regional FA value which were extracted from the significant cluster showing a TD/non-TD difference.

Results

Clinical measurements:

There was a significant group difference in the scores of PANSS_Negative (P<0.001), PANSS_Total (P=0.024), AIMS (P<0.001) and SAS (P<0.001). Schizophrenia with TD group were reported to have higher scores than Schizophrenia without TD group in these symptom severity score.

Regional FA difference among three groups:

Schizophrenia group showed lower FA in the cerebellum, temporal sub-cortical WM, parietal postcentral WM, frontal subgyral WM, and temporal sub-cortical WM than normal control (Figures 1a). TD group demonstrated more widespread FA decreases over temporal WM, parietal postcentral WM, frontal cingulated WM, sub-cortical WM, external capsule, and middle, inferior frontal gyrus WM than normal control (Fig 1b). By directly comparing the TD and schizophrenia groups, the TD group showed significantly more FA decrease over the corpus callosum, temporal WM, inferior frontal WM (around the basal ganglion), parietal precuneus gyrus WM(around somatosensory cortex), and medial frontal gyrus WM (around dorsolateral prefrontal cortex) (Fig 1c).

Correlation analysis between FA and clinical measurements:

The AIMS and SAS score was negative correlated with FA over inferior frontal WM (P<0.005) (Fig 2a), parietal precuneus WM (P<0.005), corpus callosum (P<0.005), and medial frontal WM (P<0.005). The PANSS negative score was negative correlated with FA over the medial frontal WM (P<0.005) (Fig 2b).

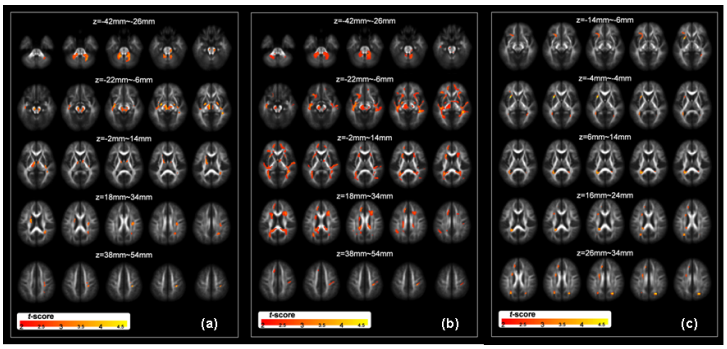
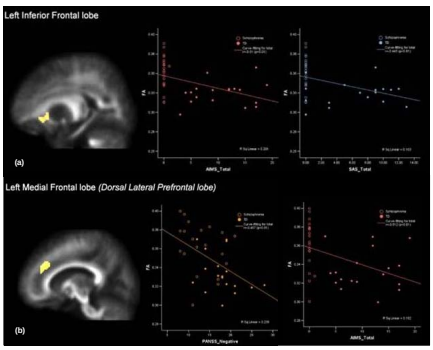


Figure 1 (a) Comparison of FA between Schizophrenia and normal groups. (b) Comparison of FA between TD and normal groups. (c) Comparison of FA between Schizophrenia and TD groups. ***Figure 2*** (a) Negative correlation between AIMS/SAS score and inferior frontal WM FA. (b) Negative correlation between PANSS/AIMS score and medial frontal WM FA.

←*Figure 1* *Figure 2*→



Conclusions

Our results showed that patients with schizophrenia had significantly lower FA over temporal, parietal and frontal WM, compared with normal controls. The result was consistent with previous results [5], and supported the hypothesis that damaged brain microcircuits might contribute to the pathophysiology of schizophrenia. We further compared the disease groups to explore the specific dysfunctional circuits in TD. The results showed significantly more FA decrease over the WM near basal ganglia, somatosensory cortex and dorsolateral prefrontal cortex. Furthermore, Negative correlations were noted between clinical ratings and these areas. The cortico-basal ganglion loop were thought to be involved in the buildup of sequential motor behavior from movement elements, as well as in goal-directed behavior. Therefore, disruption of these circuits could account for both the negative symptom and movement disorders. Our findings correlated the severity of dyskinesia and negative symptoms may support the hypotheses regarding corticobasal ganglion circuit dysfunction related to the pathophysiology of TD.

References

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