Effects of DISC1 genes on clinical symptoms and thalamic radiation in patients with schizophrenia: A tract-based diffusion spectrum imaging analysis

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Introduction

Disrupted in schizophrenia 1 (DISC1), the gene which mediates the oligodendrocytes development, plays an essential role in brain development. Previous studies reported that different types of single-nucleotide polymorphism (SNPs) in DISC1 may affect functional and anatomical connectivities of thalamo-cortical networks [1], thus conferring a genetic risk factor for schizophrenia (SZ) at the level of endophenotype. In this study, we hypothesized that different SNPs (protective form and risk form) of DISC1 would influence thalamo-cortical white matter properties, and hence the clinical symptoms of individuals with SZ. We employed diffusion spectrum imaging (DSI) to estimate the white matter property and a novel diffusion analysis pipeline called tract-based automatic analysis (TBAA) to analyze thalamo-cortical tracts.

Materials and Methods

Subjects: Twenty-nine adults with SZ (14 males; age mean: 33.52 ± 9.00 years) were recruited in this study, and they were subsequently divided into two groups according to their DISC1 genotypes (protective form *vs.* risk form). Two SNPs of DISC1 (DISC1-2 and DISC1-27) were included in this study. The severity of their clinical symptoms was evaluated by Positive and Negative Syndrome Scale (PANSS). ***MRI Data acquisition:*** All images were acquired on a 3T MRI system with a 32-channel phased-array head coil (TIM Trio, Siemens, Erlangen, Germany). DSI experiment was performed with a pulsed-gradient spin-echo diffusion EPI (TR/TE=9100/142 ms, isotropic resolution=2.5 mm, b-max=4000 s/mm^2, 102 diffusion gradient vectors). ***MRI Data analysis:*** The flow chart of TBAA was shown in Figure 1. The individual DSI images of all the subjects were first co-registered to form a study-specific template (SST) through large deformation diffeomorphic metric mapping (LDDMM), the SST were further normalized onto the NTU-DSI-122 template, a high resolution HARDI template based on 122 healthy individuals. The coordinates of the thalamic radiation (TR) on the NTU-DSI-122 template was then transferred to the SST, then to the individual datasets. The quantification parameter for white matter property, generalized fractional anisotropy (GFA), was sampled in individual's native dataset along the coordinates of the tracts. Each tract was divided into 100 steps, and GFA values within the same step were averaged. The TR was separated into 6 sub-regions according to their cortical destinations. The mean GFA of each sub-region was used for further analysis. ***Statistics:*** We separated our participants into two groups according to their genotypes, and compared their PANSS scores by independent *t*-test. We also calculated the correlations between GFA & PANSS scores with age as a covariate by Spearman correlation.

Results

Individuals with the risk form of both DISC1-2 and DISC1-27 SNPs showed significantly more severe clinical symptoms. Subjects with risk form of DISC1-27 showed higher active social avoidance ($p = 0.049$), and subjects with risk form of DISC1-2 showed higher score in hyperactivity ($p = 0.024$) and hostility ($p = 0.021$). The correlations between PANSS scores and GFA values of individuals with SZ of different SNPs exhibited different patterns in different genotypes (risk and protective). Specifically, plenty of negative correlations between white matter properties and negative symptoms were discovered in the individuals with the protective form of DISC1-27. (Figure 2).

Discussion and Conclusion

DISC1 gene influences the severity of the clinical symptoms of individuals with SZ. Higher PANSS scores in some specific subscales could be predicted in individuals with risk forms. Besides, DISC1 gene influences the white matter properties of thalamic radiation. Since all the subjects were medicated, we speculate that the negative correlations between the symptoms and the white matter properties might reflect in part the treatment effects. Individuals with the protective form of DISC1-27 seem to have a better treatment effect on negative symptoms.

References

[1] Bing Liu; DOI 10.1007/s00429-013-0640-5

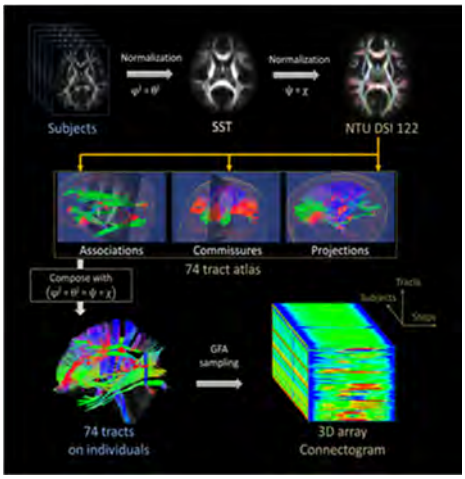

Figure 1. The flowchart of the tract-based automatic analysis (TBAA).

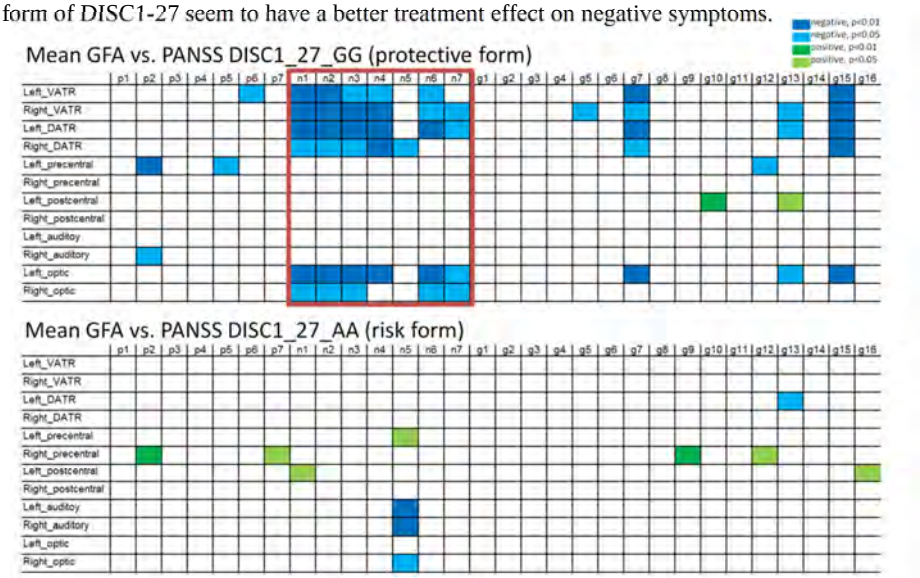

Figure 2. The correlations between PANSS scores and GFA values in individuals with SZ of different genotypes (risk and protective) exhibit different patterns. In DISC1-27, plenty of negative correlations (red square) between white matter properties and negative symptoms were discovered in individuals with the protective form.