Effects of genetic polymorphisms on white matter structure in schizophrenia measured with diffusion tensor imaging

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Introduction

Imaging provides a powerful approach to quantifying the effect of genetic polymorphisms on brain structure and function (1,2). MRI measurements of tissue volume and neuronal activation have been used as 'intermediate phenotypes' that reveal the effects of single nucleotide polymorphisms (SNPs) on specific brain structures. We studied a group of patients with schizophrenia to determine the changes in white matter structure related to polymorphisms in the histamine H_1 receptor gene. The H_1 receptor plays an important role in the control of arousal, attention, cognition, anxiety, aggression, and regulation of food intake (3). In addition, a regression analysis identified regions of white matter variability correlated with performance on neuropsychological tests.

Methods

Twenty one controls and 32 patients with schizophrenia were scanned using a 3 Tesla Philips Achieva MRI scanner. A high resolution, T1-weighted scan was performed for registration purposes and a diffusion weighted, pulsed gradient spin echo scan (92 directions, b=1000 s/mm^2, 55 slices, 2.5 mm isotropic resolution, TR = 10s, TE = 48ms, scan time 17:20) provided anisotropy information. The diffusion weighted images were corrected for eddy current distortions and head motion, and maps of fractional anisotropy (FA) were calculated using Philips PRIDE software. FA maps were registered in a common space using a multistep procedure. First, FA data were registered with a target (healthy control) high resolution T1-w dataset (using separate intrasubject T2-w to T1-w, then intersubject T1-w registration steps). FA data were averaged across subjects in the common space, yielding a mean FA template. Alignment of FA maps was significantly improved by a second stage registering individual FA data with the mean FA template. All registration steps included affine followed by nonrigid transformations (4). Genetic data were acquired for 16 patients. Effects of SNPs in the HRH1 (histamine H_1 receptor) gene were tested using a one-way ANOVA in each voxel of the common image space. The resulting statistical parametric map (SPM) was thresholded at the level $p<0.03$ and cluster size >=12 contiguous voxels. Only voxels with FA>0.2 were displayed in the SPM.

Results

Clusters of voxels in which FA varied significantly with HRH1 SNP (rs1809049) genotype were found in the inferior longitudinal fasciculus (ILF) bilaterally (Fig. 1), the anterior corticospinal tract (CST) bilaterally, and the right posterior limb of the internal capsule (PLIC). Clusters of white matter voxels with significant dependence on the genotype of a second HRH1 SNP (t102c htrs2a) were found in the brainstem bilaterally. Other regions were found to correlate with tests of executive function (right forceps minor, anterior thalamic radiation) and psychopathology (left superior thalamic radiation/ internal capsule).

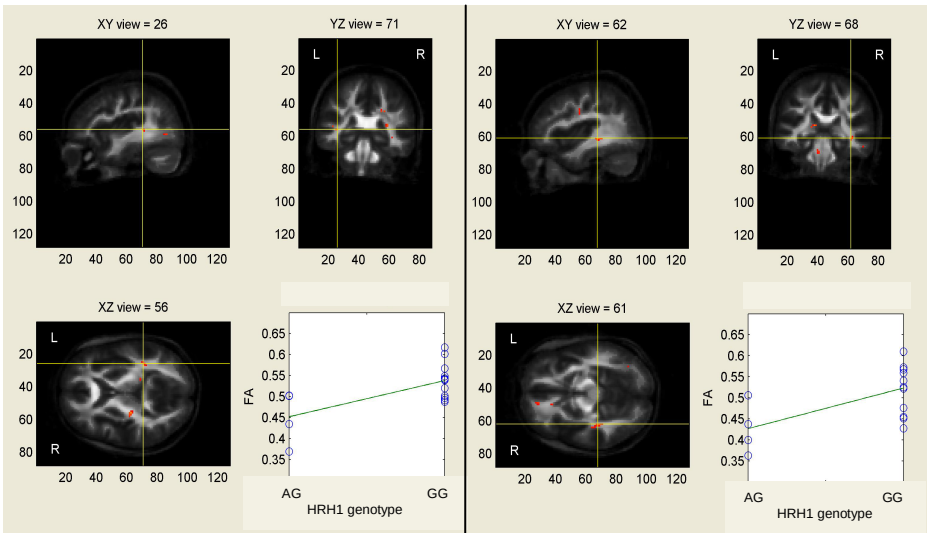

Figure 1. Histamine H_1 receptor gene (HRH1) polymorphisms affect white matter structure in the inferior longitudinal fasciculus bilaterally ($p<0.015$; left hemisphere is shown in the left panel, right hemisphere in the right panel).

Conclusions

Polymorphisms in the histamine H_1 receptor gene are associated with variations in fractional anisotropy in specific regions of brain white matter. These could reflect changes in the intrinsic diffusivity of fiber bundles (e.g., axonal packing or myelination) or larger-scale differences in fiber pathways and crossing patterns. In any case, the genetically-driven differences in white matter structure may provide a new understanding of genotypic effects on behavior in terms of deficits in specific fiber bundles. Hence, diffusion MRI studies of white matter fiber structure could yield new information on the causal relationship between genes and disease symptoms.

References

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