BDNF Effects on Brain Fiber Microstructure Replicated in Two Twin Samples (N=455)

Abstract No:

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Introduction:

Brain-derived neurotrophic factor (BDNF) is critically involved in learning and memory, as it modulates hippocampal neurogenesis, synaptic transmission, and activity-induced long-term potentiation and depression. The methionine (Met) for valine (Val) substitution at codon 66 in the 5′-proregion of the BDNF protein (Val66Met; dbSNP number rs6265), a common variant in the BDNF gene, has been associated with poorer episodic memory and lower hippocampal BOLD activity (Egan et al., 2003). To study how this polymorphism affects fiber integrity, and replicate it in an independent sample, we acquired diffusion tensor images (DTI) from two independent samples of 234 and 221 twins and their siblings. By applying the QTDT association method (Abecasis et al., 2000) at each voxel, we mapped the associations between the BDNF polymorphism on brain white matter anisotropy, extending single-gene association analyses to 3D images.

Methods:

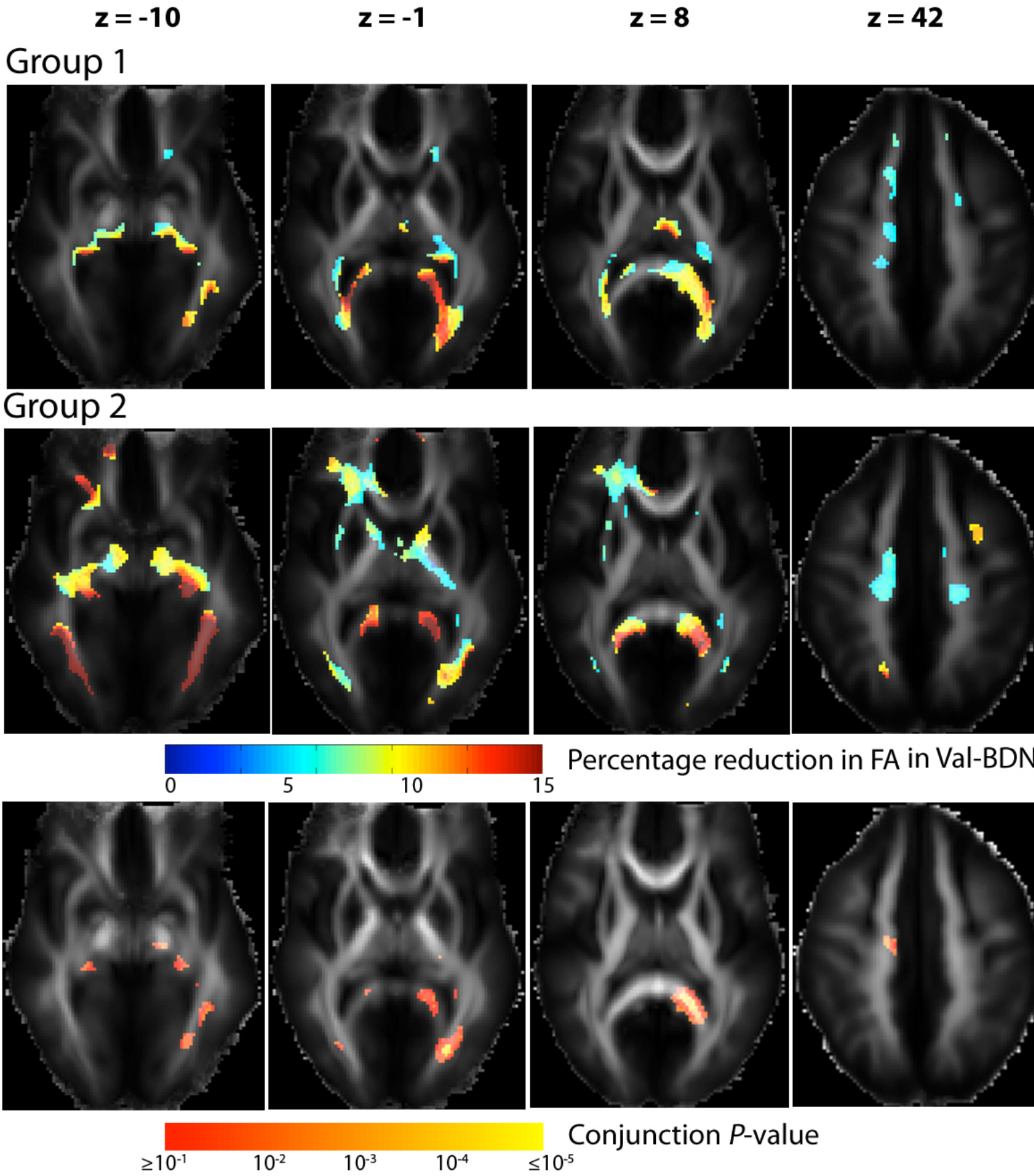
We acquired 30-gradient DTI at 4 Tesla from 234 subjects (denoted by Group 1; 99 males/135 females; age: 23.7±1.9 years, mean±SD) from 110 different nuclear families. BDNF genotypes were Val/Val for 161 (68%), Val/Met for 60 (26%), and Met/Met for 13 subjects (6%). To replicate our findings in a separate, independent sample, we conducted a second association study by identically scanning 221 subjects (Group 2; 89 males/132 females; age: 23.7±2.2 years) from 128 families unrelated to those in Group 1. BDNF genotypes were Val/Val for 155 (70%), Val/Met for 58 (26%), and Met/Met for 8 subjects (4%). This BDNF genotype distribution in both groups followed the Hardy-Weinberg equilibrium. High angular resolution diffusion-weighted scans were acquired using single-shot echo planar imaging with a twice-refocused spin echo sequence, to reduce eddy-current induced distortions. Imaging parameters were: 21 axial slices (5 mm thick), FOV = 23 cm, TR/TE 6090/91.7 ms, 0.5 mm gap, with a 128x100 acquisition matrix. 30 images were acquired: 3 with no diffusion sensitization and 27 diffusion-weighted images (b = 1145.7 s/mm²). The reconstruction matrix was 128x128, yielding a 1.8x1.8 mm² in-plane resolution. Total scan time was 3.05 minutes. We used the FSL software package (http://www.fmrib.ox.ac.uk/fsl/) for pre-processing and affine alignment of the diffusion images. The FA image derived from the affine-registered DT image was then fluidly registered to a randomly selected subject's FA image. We then analyzed within-family associations between the BDNF polymorphism and FA at each voxel, using the QTDT method. The model included the additive effects of the BDNF polymorphism, the residual additive polygenic effects, and environmental effects that are common to all family members and that are specific for each individual. Multiple comparisons across voxels were corrected using the "searchlight" false discovery rate (FDR) method (Langers et al., 2007).

Results:

The upper and middle rows of Figure 1 (MNI coordinates of the slices, expressed in mm, are shown at the top) show that, in both Groups 1 and 2, the Val allele of BDNF was associated with up to 15% reduction in FA in the splenium of the corpus callosum on the left and left optic radiation, inferior longitudinal fasciculus on the left, midbrain and fornix bilaterally, and superior corona radiata on the right. To better visualize the regions where the BDNF-FA association is significant in both subject groups, we conjoined the two significance maps for Groups 1 and 2 by taking the larger voxelwise P-value of the two groups. The conjunction P-maps are displayed on a log10 scale (lower row). These findings suggest that variants in the BDNF gene may influence several key white matter regions, especially the splenium of the corpus callosum and the left optic radiation. Significant associations were discovered and replicated in independent samples.

Conclusions:

We visualized associations between common BDNF gene variants and brain fiber architecture by analyzing the FA images of twins and non-twin siblings. Based on two independent twin subject samples, and a conjunction of both association maps, the Val allele was associated with up to 15% reduction in FA in major fiber tracts. BDNF is a candidate gene with critical influences on white matter microstructure.



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Categories

- Genetics (Genetics)
- Diffusion MRI (Imaging Techniques and Contrast Mechanism)
- DTI Studies, Application (Neuroanatomy)