Multi-SNP Effects on Temporal Lobe Structure Replicated in ADNI (N=738) and Queensland Twins (N=568)

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Introduction:

As genetic variants associated with brain structure continue to be discovered through neuroimaging, one can study the aggregate effect of candidate variants on voxelwise maps of the brain. Here, we investigate the combined effect of top single nucleotide polymorphisms discovered by Stein et al. in a temporal lobe volume genome-wide association study (GWAS) on temporal lobe maps in the original ADNI cohort and a replication sample of young adult twins and siblings.

Methods:

Subjects: 738 Caucasian ADNI subjects, (173 with AD; age: 75.6 ± 7.6 years, 359 with MCI; age: 75.1 ± 7.2 years, and 206 healthy controls; age: 76.1 ± 5.0 years), as well as 568 healthy young adult twins and siblings of European descent (age: 23.8 ± 2.2 years) were considered in this study.

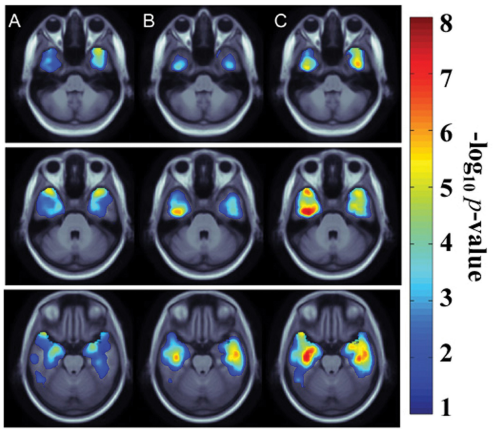
Brain Imaging: ADNI subjects were scanned with 1.5-Tesla MRI and the young adults were scanned with 4-Tesla MRI. Tensor-based morphometry is implemented for the study of voxelwise volumetric differences in the temporal lobes.

Genetic variants: Top 2 single nucleotide polymorphisms (SNPs) from Stein et al.'s 2010 GWAS (rs10845840 in the *GRIN2B* gene, and the intergenic rs2456930 polymorphism) were considered as candidate variants in this study.

Statistics: Single and multi-SNP *p*-values were obtained at each voxel for the associations with temporal lobe volumetric differences. Sex and age were considered as covariates; population structure was an additional covariate for the ADNI cohort; kinship structure was also taken into account for the twins and siblings using mixed-effects modeling. All *p*-value maps were corrected for multiple comparisons using a regional false discovery rate (FDR) method.

Results:

Figure 1: Multi-SNP effects on temporal lobes (elderly ADNI cohort)



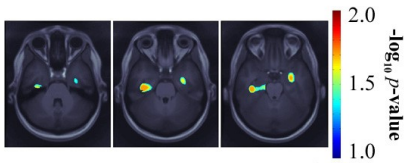
When considered independently, the intronic *GRIN2B* polymorphism, rs10845840, (the top hit in Stein et al.'s temporal lobe GWAS) was significantly associated with 52% of temporal lobe voxels, mostly in the medial temporal lobe regions and the poles (representative axial slices shown in **Figure 1A**), as reported previously by Stein et al. (2010).

The intergenic, predicted regulatory rs2456930 polymorphism was significantly associated with 45% of temporal lobe voxels as shown in three axial slices in **Figure 1B**.

In a joint (multi-SNP) model, the rs10845840 and rs2456930 polymorphisms were more strongly and significantly associated with nearly 65% of the temporal lobe voxels (**Figure 1C**). All associations were adjusted for sex, age and population structure in the ADNI population; *p*-values shown are corrected for multiple comparisons with a regional FDR method.

Figure 2 shows voxelwise significance of the joint effect of rs10845840 and rs2456930 in the healthy young twins and siblings. After correction for multiple comparisons, we found reproducibility for the anatomical scope of the multi-SNP effects in the young adult cohort. The associations were particularly strong in the medial regions of the temporal lobes. Unlike in the ADNI cohort, the majority of the contribution here was from the rs2456930 SNP.

Figure 2: Multi-SNP effects on temporal lobes (young adult cohort)



Conclusions:

We were able to find extensive, genetic influence on the voxelwise maps of temporal lobes in an elderly population by incorporating two top genetic variants from a prior GWAS study. The multi-SNP model was also significantly associated with medial temporal lobe voxels in a replication sample of young adults. The multi-SNP effects may have implications on brain disorders such as Alzheimer's disease and schizophrenia, where temporal lobes are affected.

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