Genome-wide polygenic risk for AD is associated with rate of atrophy in the hippocampus

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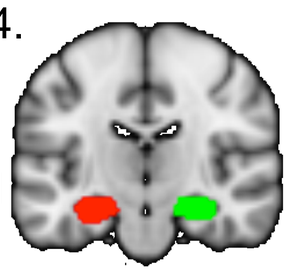
Background

Genome-wide association studies (GWAS) have revealed numerous genetic loci that are consistently associated with the risk to develop late-onset Alzheimer's disease (AD). Genome-wide polygenic scores (**GPS**) for diseases and traits are a recent development in statistical genetics and allow **aggregating the genetic risk into one single score**. In previous studies, an AD-GPS showed consistent and strong association with the disease in independent subjects. Here we analyzed the association of an AD-GPS with the rate of hippocampal atrophy in a study sample from the Alzheimer's disease neuroimaging initiative (ADNI).

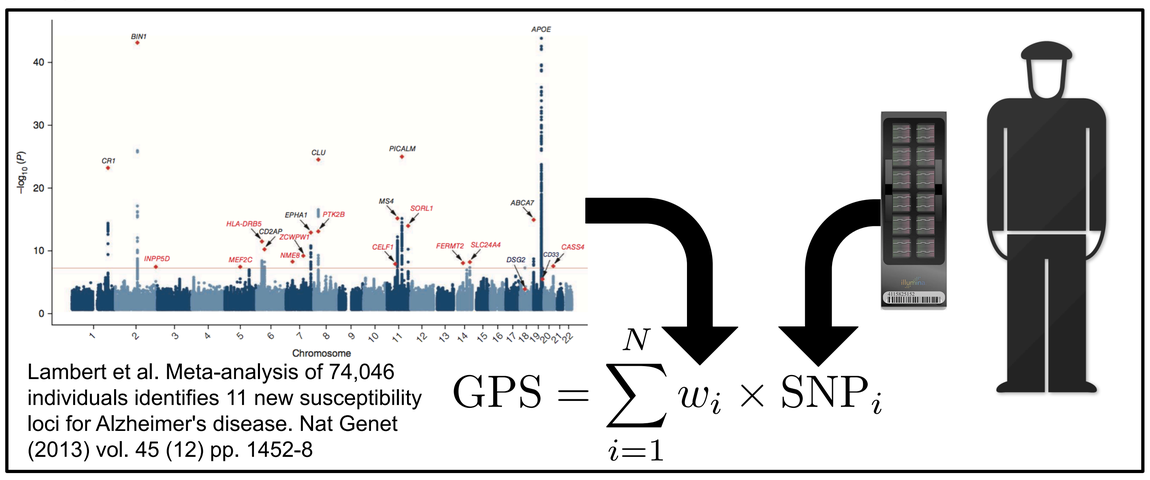
Methods

Study sample: We used 652 subjects from the ADNI database with T1 weighted structural brain scans obtained using a 3T scanner and available genome-wide single nucleotide polymorphism (SNP) data. None of the subjects contributed to the large GWAS used for the GPS computation. The final set comprised 179 healthy controls, 378 MCIs and 94 AD subjects. The number of scans per subject ranged from 2 to 6 with a median of 4.

Estimates of hippocampal volume for the left and right hippocampi were based on manual segmentations the volumes were normalized using total intracranial volume (TIV).



GPS construction: The GPS is a weighted sum of the number of risk alleles present in a subject (SNP_i). The weights (w_i) are obtained from the summary statistics of a large GWAS.

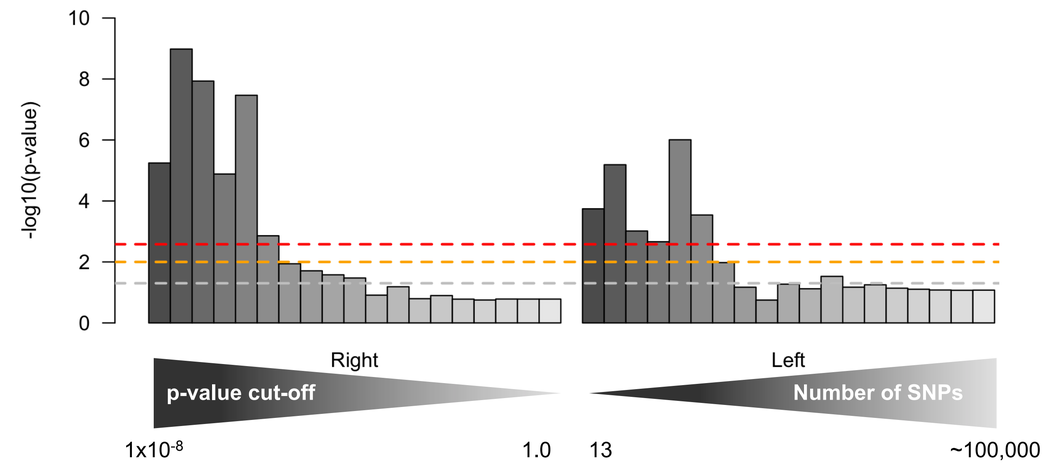


The extended APOE locus was excluded from the GPS. We computed GPS for 19 p-value cutoffs in the range from 1 x 10^{-8} to 1.0.

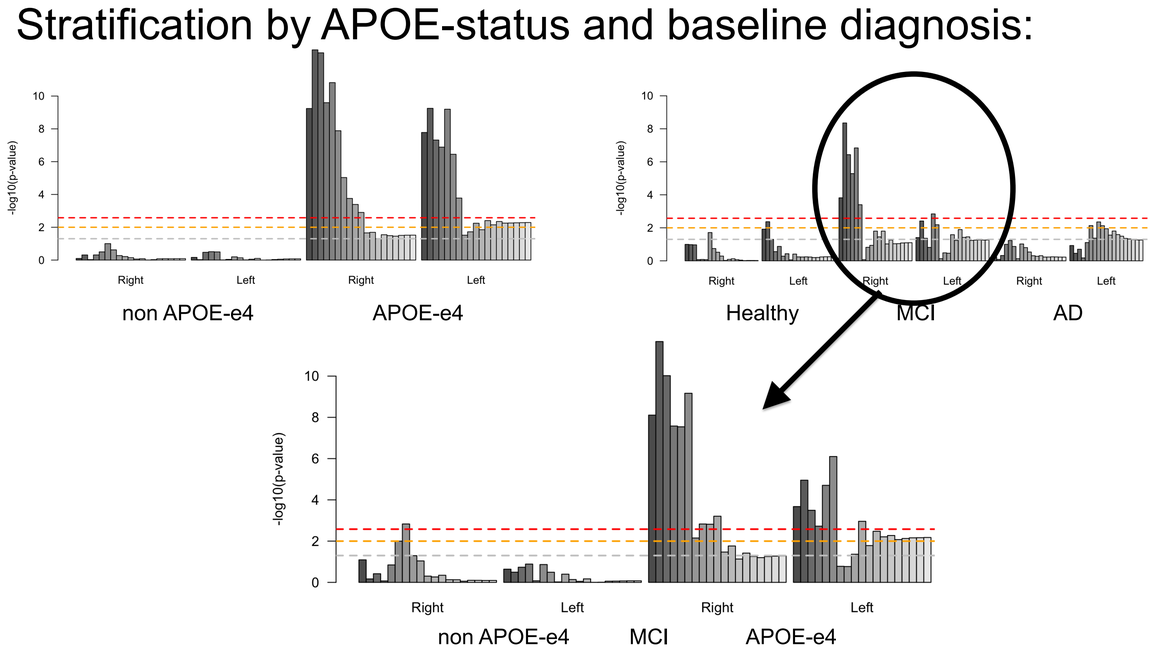
Statistical analysis: The effect of the GPS on rate of hippocampal atrophy was estimated using a linear mixed effects model using following fixed effects: diagnosis and age at baseline scan, sex, years of education, population structure (3 PCs), APOE-e4 status, GPS, time since baseline scan (t) and interactions between APOE-e4 status and t and between GPS and t. **We tested for a non-zero coefficient for the interaction between GPS and *t*.**

Results

GPS containing few significant SNP are significantly associated with rate of atrophy in both hippocampi.



Stratification by APOE-status and baseline diagnosis:

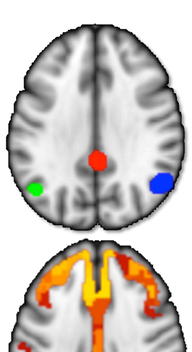


The APOE-dependent association remains after restricting the analysis to MCI subjects.

Conclusions

There is a significant association between the AD-GPS and the rate of hippocampal atrophy. Notably, the significant effect of the GPS was driven by APOE-e4 carriers. This observation is consistent with findings of APOE-e4 leading to a more hippocampal focused disease. This potential interaction between polygenic AD risk and APOE clearly warrants further investigations.

Bonus Results



- AD-GPS is associated with rate of metabolic decline (measured with FDG-PET) – but mainly in non-APOE4 carriers.
- AD-GPS is not associated with rate of brain amyloid increase (measured with AV45-PET)

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