Voxelwise Genome-Wide Association Study (vGWAS)

Abstract No:

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Introduction:

Recent advances in neuroimaging and genetics have made it possible, and financially feasible, to scan populations with multi-modality brain imaging and collect genome-wide genotype data [1,2]. The Alzheimer's Disease Neuroimaging Initiative (ADNI) recently acquired genome-wide genotype data and structural MRI scans from 818 subjects. This wealth of data presents powerful and unprecedented spatial and genetic resolution to detect specific variants that influence the brain. However, it requires new ways to deal with the computational load and account statistically for multiple comparisons across the genome and across the images. For the first time, we conducted a voxelwise genome-wide association study (vGWAS) to discover genes influencing brain structure across the entire brain. Each genetic variant identified is a potential candidate with the ability to affect brain structure.

Methods:

Neuroimaging and genetic data were acquired from 818 subjects as part of the Alzheimer's Disease Neuroimaging Initiative (www.loni.ucla.edu/ADNI). Only unrelated Caucasian subjects (non-Hispanic; N=740) identified by self-report and confirmed by MDS analysis were included to reduce population stratification effects. Volumetric brain differences were assessed in 173 AD patients (78 female/95 male; mean age ± standard deviation = 75.54 ± 7.66), 361 MCI subjects (130 female/231 male; 75.16 ± 7.29), and 206 healthy elderly subjects (112 male/94 female; 76.13 ± 4.94). 3D T1-weighted baseline brain MRI scans were analyzed using tensor-based morphometry (TBM) to measure volume differences relative to a standard template [3,4].

Genome-wide genotype information was collected at 620,901 markers. We conducted a genome-wide association analysis using volume differences relative to a mean brain image template at each voxel as a phenotype, assuming an additive genetic model and controlling statistically for age and sex. We selected only the most associated SNP at each voxel, saving its P-value and identifier. The effective number of tests was calculated by determining the number of principal components that explained 99.5% of the genotypic variance [5]. P-values were corrected across SNPs with a transformation using the CDF of an analytic Beta distribution with parameter estimated by the effective number of tests (Figure 1). "Corrected" P-value maps were assessed for how they controlled the false discovery rate, using various implementations of the FDR theory to correct for multiple comparisons across voxels.

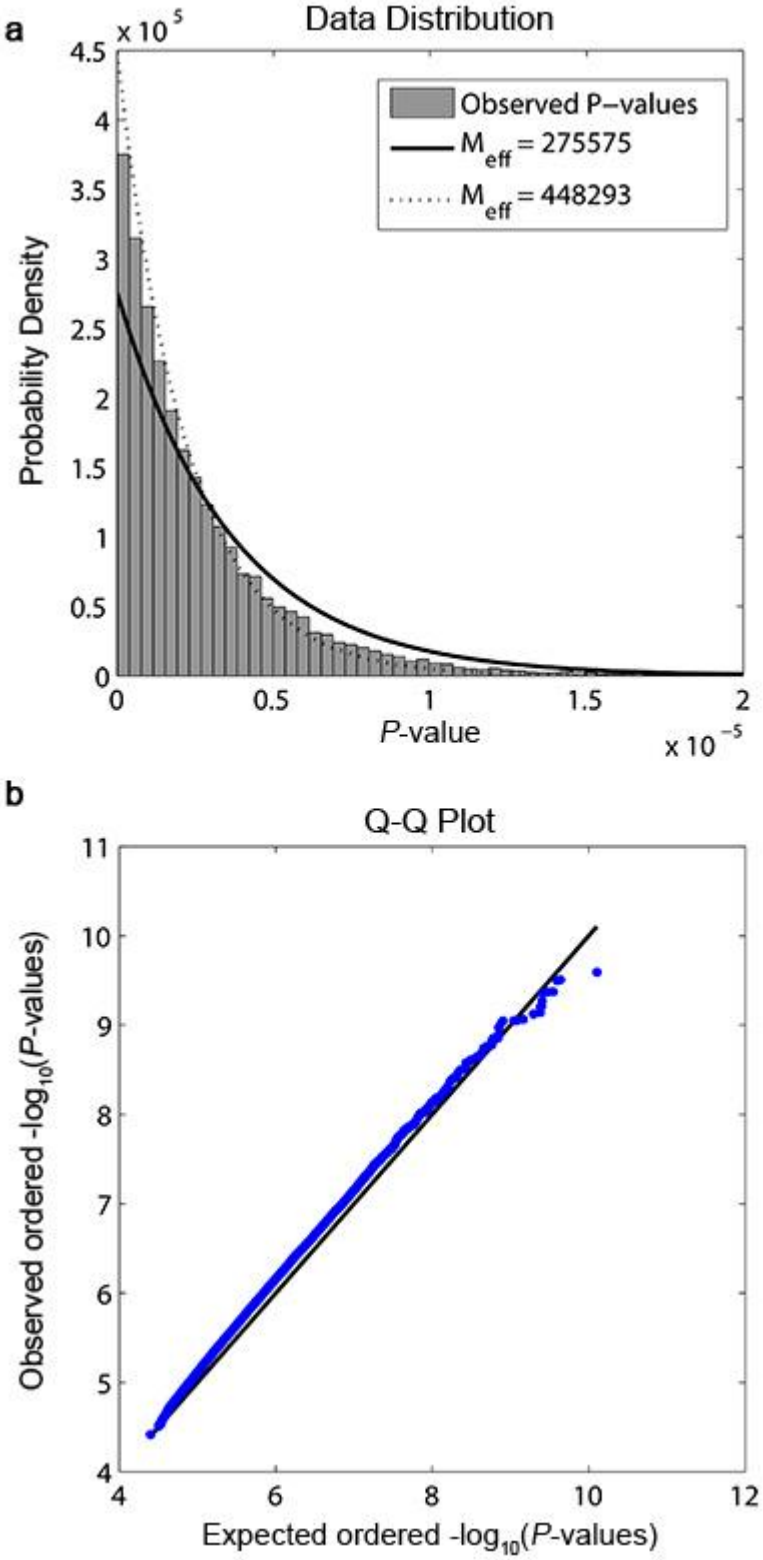
Results:

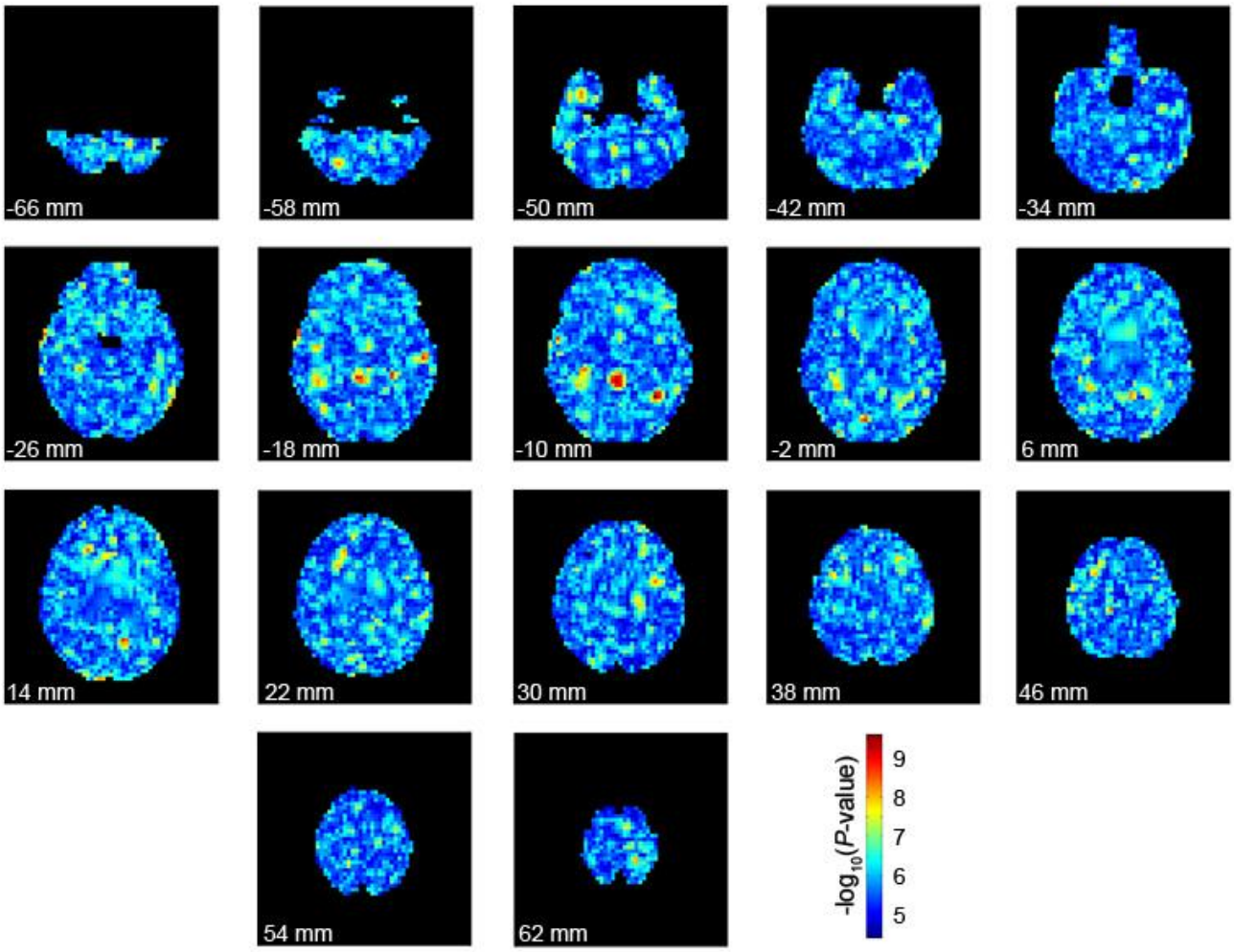
Figure 2 shows maps of the significance level at each voxel for the most associated SNP within that voxel. There are spatially contiguous hot spots of significant association, with a "raw" minimum P-value of 2.56x10^-10 ("corrected" P-value = 7.05x10^-5) across the entire brain. The pFDR threshold gives a q-value of 0.25 for the most associated voxel of SNP rs2132683. The voxelwise GWAS showed 8,212 unique SNPs that were most associated at some voxel. In other words, if the "winning SNP" was picked for each voxel, the same SNP was picked over spatially coherent regions. Locations of the winning SNPs are displayed for the top 5 SNPs in Figure 3. Two interesting SNPs identified were rs476463 and rs2429582. SNP rs476463 is located within an intronic region of the CSMD2 gene. CSMD2 has highest expression in the brain and may be a oligodendroglioma suppressor [6], though the function of the protein is largely unstudied. Additionally, it has been associated with ADHD [7] and addiction. The allele frequency of this SNP did not statistically differ between diagnostic groups (AD and MCI: 0.116; healthy elderly: 0.131; P = 0.428; OR = 0.871). SNP rs2429582 is located within an intronic region of the CADPS2 gene and is the SNP that associated with brain structure the most in the lateral temporal lobe. This gene regulates synaptic and large dense core vesicle priming in neurons [8], especially promoting monoamine uptake and storage in neurons. CADPS2 is strongly expressed in the brain, specifically in cerebellum, cortex, olfactory bulb, hippocampus, striatum, thalamus, and superior and inferior colliculi. The gene is located in an area with known linkage to autism [9]. Splice variants of this gene may also be relevant to autism, though there is some controversy over this finding [10]. The allele frequency for this SNP had a trend level difference between diagnostic groups (AD and MCI: 0.355; healthy elderly 0.307; P = 0.084; OR = 1.24).

Conclusions:

Genome-wide association using brain phenotypes in humans has only been started in a few previous studies, to our knowledge. These studies used drastic data reduction and only studied gross phenotypes of interest like total cranial, lobar, ventricular, or hippocampal volumes. Our analysis offers a conceptual advantage as it searches for voxelwise genetic associations in 3D, which should offer much greater anatomical detail about genomic association, with potentially higher statistical power. Using this method, we found several genes with high relevance to brain structure. Specifically, CADPS2 is involved with monoamine uptake in neurons; CSMD2 and CADPS2 have been associated with psychiatric illness; and SHB and FARP1 are associated with

neurite growth. Given this prior information on how these genes function on the brain, it is likely that some of the genetic variants found here have important effects on the structure of the brain.

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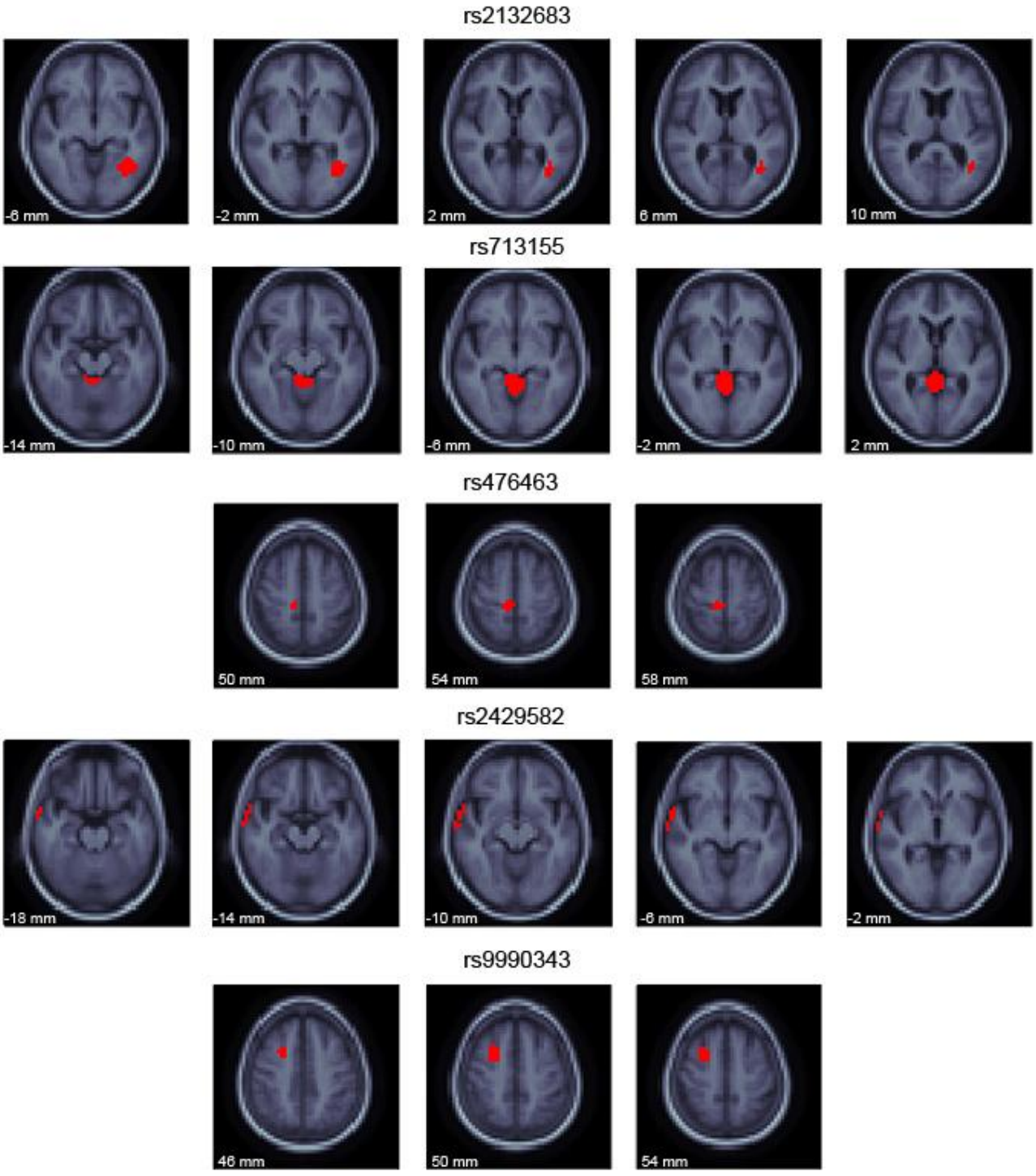

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Categories

- Alzheimer and Dementia (Disorders of the Nervous System)
- Genetics (Genetics)
- Anatomical MRI (Imaging Techniques and Contrast Mechanism)