Whitematter hyperintenisties, *MTHFR* gene and Brain volumes in 509 Cognitively impaired ADNI subjects

Priya Rajagopalan[1], Neda Jahanshad[1] Arthur Toga[1], Clifford Jack[2], Michael Weiner[3, 4], Paul Thompson[1] and the Alzheimer's Disease Neuroimaging Initiative

[1]Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Los Angeles,
[2]Department of Radiology, Mayo Clinic, Rochester, Minnesota, [3]Department of Radiology, Medicine, and Psychiatry, University of
California San Francisco and
[4]Department of Veterans Affairs Medical Center, San Francisco, California, USA

INTRODUCTION

Carriers of a common folate pathway genetic variant – a single nucleotide polymorphism (SNP) C677T in the methylenetetrahydrofolate reductase gene – have higher plasma levels of homocysteine (Hcy). This SNP (rs1801133) is also associated with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Plasma Hcy, through its vascular effects or direct neurotoxicity, is a known risk factor for poor cognitive performance and is associated with both severe white matter hyperintensities (Wmh) and brain atrophy. It is also shown that C677T gene variant (T, Minor allele frequency 0.3) is associated with severe white matter hyperintensity burden and white matter burden is in turn associated with brain volumes. We therefore set out to test whether the risk allele of this SNP is associated with lower volumes, especially in regions where brain atrophy is related to Wmh, in a large cohort of subjects with cognitive impairment.

METHODS

Our data consisted of 509 Caucasian subjects (157 AD, 347 MCI; mean age: 75.3+/-6.8 years) scanned with brain MRI at 1.5 Tesla and genotyped as part of Alzheimer's Disease Neuroimaging Initiative. Using tensor-based morphometry, we generated 3D Jacobian maps of regional brain volume differences, by mapping subjects to a cohort-specific mean template (MDT). We then created 3D maps to show regions of volume deficit or excess relative to the brain template, reflecting, in part, profiles of neurodegeneration. We used a standard false discovery rate (FDR) correction for multiple statistical comparisons across all voxels in the brain, at the conventionally accepted level of $q = 0.05$.

We first carried out standard linear regression at each voxel, to associate wmh volumes against brain structure after controlling for both age and sex. We then examined associations between the C677T genotype and regional brain structure using multiple regression, controlling for age and sex, using the additive effect of *MTHFR* risk alleles (number of T alleles in the SNP coded as 0,1, or 2). Tests for the SNP associations were conducted at all brain voxels, and also specifically in wmh-associated brain regions with a p-value < 0.05.

RESULTS

Wmh volumes were significantly associated with brain volume deficits of up to 1% in the peri-ventricular white matter regions, after adjusting for age and sex.

The statistical association maps derived for the *MTHFR* genotype, showed that the risk allele was associated with regional brain atrophy in regions where atrophy was associated with wmh volumes. Brain volume deficits of up to 6% per T allele relative to the MDT were found in the bilateral fronto-parietal white matter (a critical p-value of 0.002 controlled the standard false discovery rate at the 5% level).

Table 1

Mean (Standard error)	CC (Homozygous non-risk genotype)	CT (Heterozygous risk genotype)	TT (Homozygous risk genotype)
Sample size (n)	218	209	72
Age (years)	75.2 (0.5)	75.3 (0.5)	75.6 (0.9)
Sex (Men, Women)	124, 95	137, 73	43, 29
Education (years)	15.3 (1.0)	15.3 (0.2)	15.1 (0.3)
BMI[α] (kg/m^2)	25.9 (0.3)	26.2 (0.05)	25.1 (0.3)
Systolic BP[β] (mmHg)	134.5 (1.1)	133(1.2)	130.6 (1.9)
Diastolic BP[β] (mmHg)	74.3 (0.6)	73.1 (0.7)	72.8 (1.0)
White matter hyperintensity	0.90 (0.1)	1.2 (0.2)	0.96 (0.3)
Homocysteine[γ] (μmol/L)	10.4 (0.2)	10.5 (0.2)	11.9 (0.05)
MMSE[δ]	25.7 (0.2)	25.9 (0.2)	26.2 (0.3)
Global CDR[ε]	2.5 (0.2)	2.4 (0.1)	2.5 (0.2)
ApoE4 ε4 (0,1,2)	89, 111, 30	93, 91, 38	39, 2, 9

[α]body mass index
[β]blood pressure
[γ]Baseline morning fasting plasma levels
[δ]mini-mental status examination (maximum score: 30)
[ε]clinical dementia rating

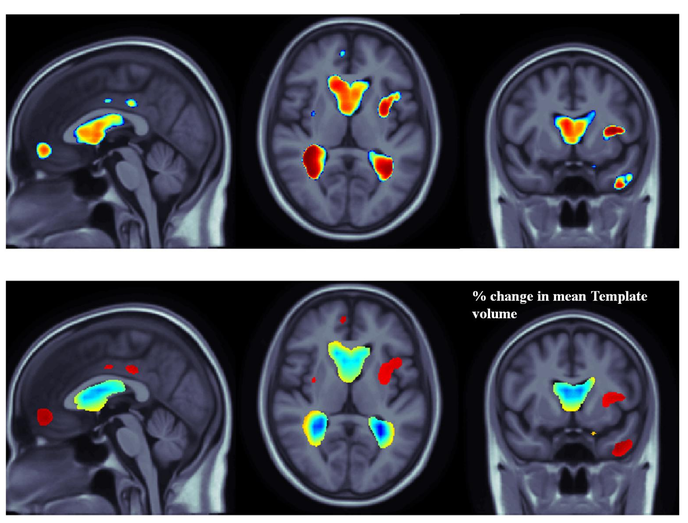

Figure 1. (Top) 3D p-value maps displayed over the minimal deformation template (MDT) show areas where the white matter hyperintensities is significantly (thresholded for FDR crticial p-value 0.0019) associated with regional brain volume differences in cognitively impaired ADNI subjects (n = 504) after covarying for age and sex. (Bottom) In the significant brain regions, 3D Beta-value maps show the estimated regional brain volume deficit of up to 1% relative to the MDT in the significant voxels per unit increase in the white matter hyperintensity volume, in the same subjects.

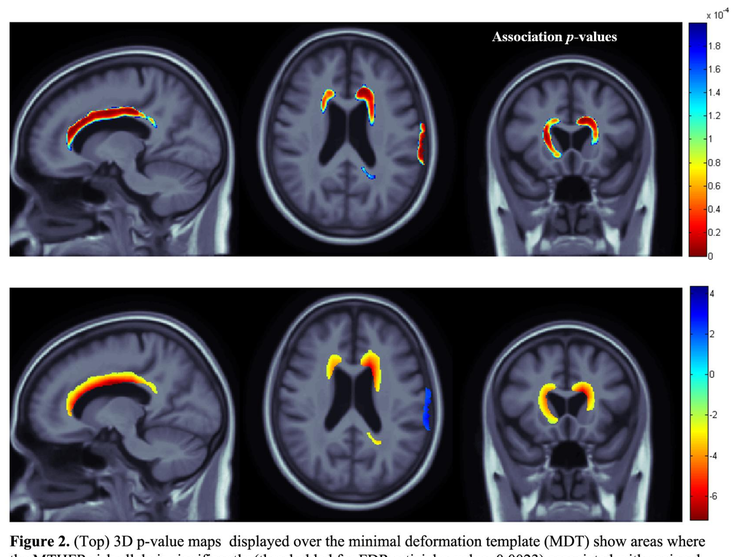

Figure 2. (Top) 3D p-value maps displayed over the minimal deformation template (MDT) show areas where the MTHFR risk allele is significantly (thresholded for FDR crticial p-value 0.0023) associated with regional brain volume differences in cognitively impaired ADNI subjects (n = 504) after covarying for age and sex. (Bottom) In the significant brain regions, 3D Beta-value maps show the estimated regional brain volume deficit of up to 6% relative to the MDT in the significant voxels per unit increase in the risk allele, in the same subjects.

CONCLUSION

We discovered that the *MTHFR* gene variant and white matter hyperintensities influence atrophy in similar brain regions. This is the first study to map the *MTHFR* effect on brain structure which may be due to wmh burden association with the risk allele. It is plausible that wmh affects brain structure and *MTHFR* may be a contributing cause of this association (but probably not the only cause). The *MTHFR* risk allele may also directly affect brain structure independent of the wmh pathway. Further investigation relating MTHFR gene polymorphisms, wmh, and brain atrophy is warranted.

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