



Folate pathway gene variant and Homocysteine: associated with volume deficits in similar brain regions



Priya Rajagopalan¹, Neda Jahanshad¹, Jason L. Stein¹, Omid Kohannim¹, Derrek P. Hibar¹, Arthur W. Toga¹, Michael W. Weiner², Clifford R. Jack Jr.³, Andrew J. Saykin⁴, Robert C. Green⁵, Paul M. Thompson¹, and the Alzheimer's Disease Neuroimaging Initiative (ADNI)

¹Laboratory of NeuroImaging, UC Los Angeles, California, ²UC San Francisco, Department of Veterans Affairs Medical Center, California, ³Mayo Clinic, Rochester, Minnesota, ⁴Indiana University School of Medicine, Indianapolis, ⁵Boston University, Massachusetts.

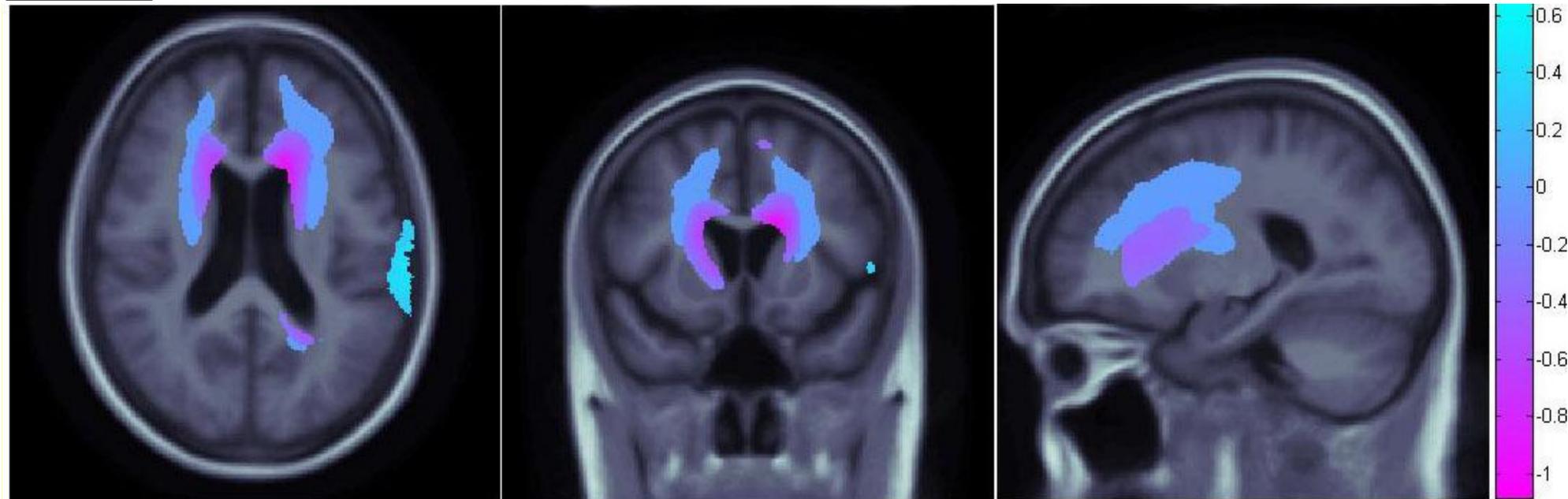
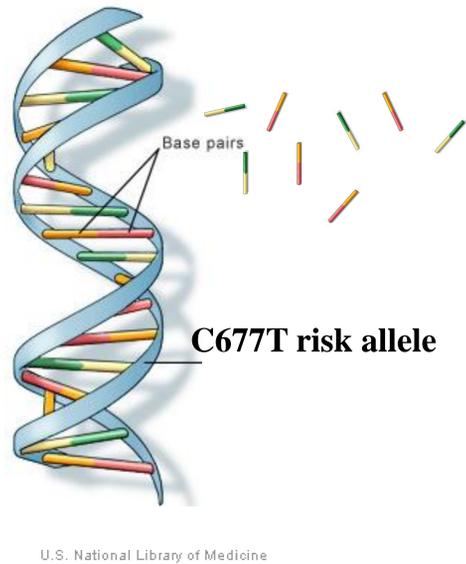
INTRODUCTION

Carriers of a common single nucleotide polymorphism (SNP) C677T in the *MTHFR* (methylenetetrahydrofolate reductase) gene - have higher plasma levels of homocysteine (Hcy). Hcy, through its vascular effects or through direct neurotoxicity, is associated with lower regional brain volumes.

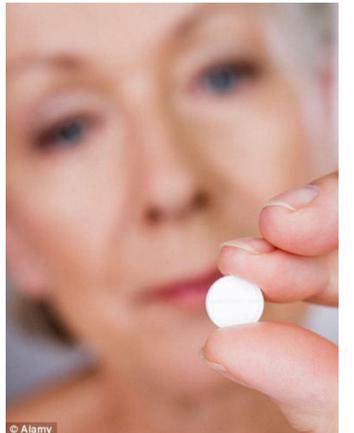
METHODS

Our data consisted of 529 Caucasian subjects (173 AD, 356 MCI; mean age: 75.3+/-6.8 yrs) scanned with brain MRI at 1.5 Tesla and genotyped as part of ADNI. Using tensor-based morphometry, we generated 3D Jacobian maps of regional brain volume differences by mapping subjects' scans to a cohort-specific mean template (MDT). We then carried out standard linear regression at each voxel, to associate plasma Hcy levels with brain atrophy. We also correlated the number of T alleles in the SNP (0,1, or 2) to volume differences in Hcy-related brain regions, after adjusting for age, sex, and diagnosis (AD/MCI).

RESULTS



3D Beta-coefficient maps displayed over the mean template show areas where brain volume deficits relative to the MDT of up to 0.75% deficit per T allele in the C677T SNP (pink, FDR critical *P*-value 0.0033) and Homocysteine (blue, FDR critical *P*-value 0.0056) in ADNI subjects with cognitive impairment (n=529) after statistically controlling for age, sex and diagnosis (AD/MCI).



Courtesy of iStockphoto.com
Vitamin B supplements

pria@ucla.edu

HYPOTHESIS

We therefore set out to test whether the risk allele (T, minor allele frequency 0.3) of the SNP is associated with lower brain volumes, especially in regions where brain atrophy is related to Hcy, in a large cohort of subjects with cognitive impairment.

CONCLUSION

We discovered that the *MTHFR* variant, possibly mediating its effects through Hcy, influences volume deficits in similar brain regions as Hcy. This motivates studies of dietary vitamin B supplements that may modulate gene effects and reduce Hcy levels, with the goal of resisting cognitive decline.