Homocysteine effects on brain volumes: Mapped in 732 elderly individuals

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INTRODUCTION

Elevated homocysteine levels are a known risk factor for Alzheimer's disease and vascular disorders. Here we applied tensor-based morphometry to brain magnetic resonance imaging scans of 732 elderly Caucasian subjects from the Alzheimer's Disease Neuroimaging Initiative study, to determine associations between homocysteine and brain atrophy.

	AD	MCI	Controls	Entire cohort
Sample size (n)	**173**	**356**	**203**	**732**
Age (years)	**75.6±7.6**	**75.2±7.3**	**76.1±5.0**	**75.5±6.8**
MMSE*	**23.4±2.0**	**27.1±1.8**	**29.2±1.0**	**26.8±2.7**
Plasma homocysteine (μmol/L)	**10.8±3.3**	**10.7±2.8**	**10.0±2.9**	**10.5±3.0**

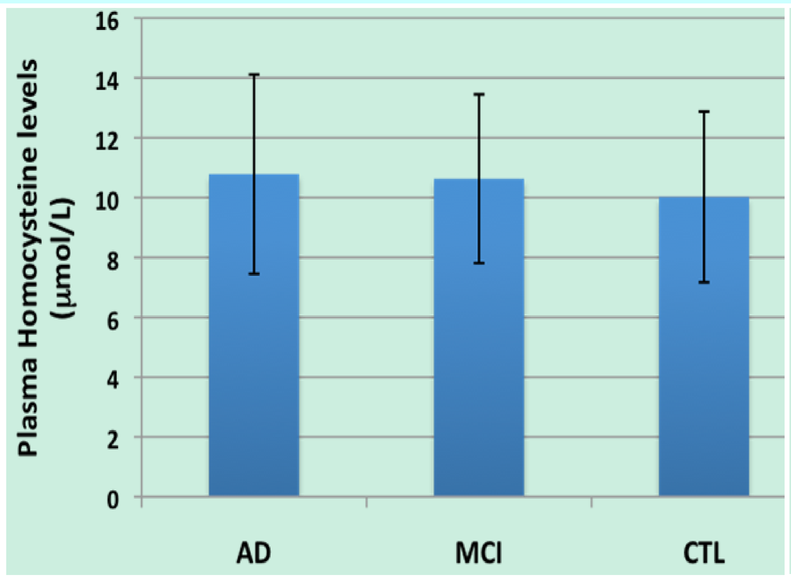
*Mini Mental State Exam; maximum score is 30; AD- Alzheimer's disease, MCI – mild cognitive impairment

METHODS

732 elderly subjects (203 healthy controls, 356 with mild cognitive impairment (MCI) and, 173 with AD; mean age: 75.5 +/- 6.8 years) received an MRI at 1.5 Tesla as part of the ADNI. Homocysteine levels were estimated from blood plasma collected after overnight fasting. Using Tensor-Based Morphometry [TBM] 3D maps were created to show regions of volume deficit or excess relative to the brain template based on 40 healthy elderly subjects. At each voxel within the brain, multiple regression was carried out to analyze statistical associations between regional brain volumes and plasma homocysteine levels. 3D maps were created 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 voxels of the brain, at the conventionally accepted level of q = 0.05.

RESULTS

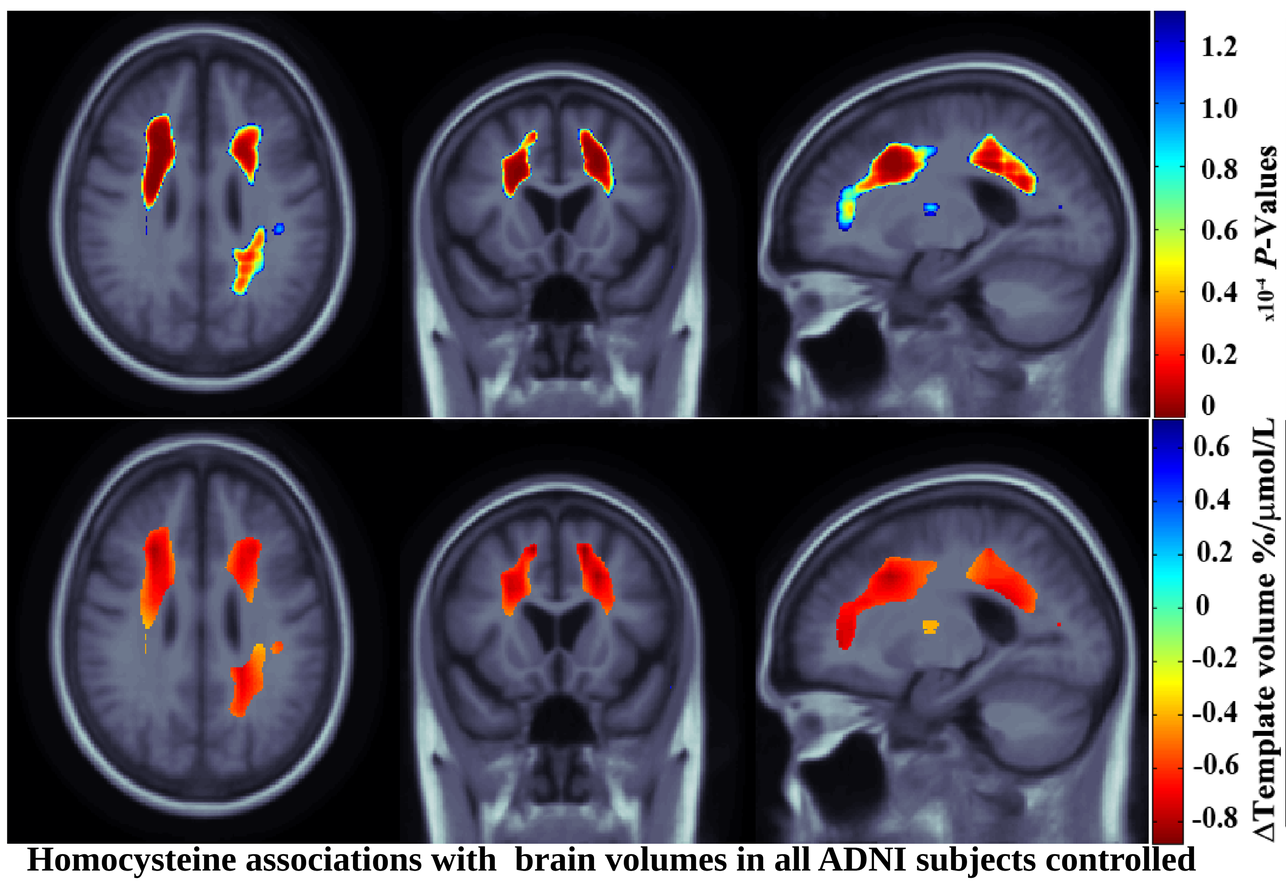
Compared to the healthy controls, the levels of homocysteine were significantly higher in subjects with AD (two-tailed t-test, p=0.018) and MCI (two-tailed t-test p= 0.015). Linear regression analysis showed significant brain associations with homocysteine levels in ADNI subjects, even after covarying for age, sex and disease status. After correcting for multiple statistical comparisons (FDR, q = 0.05, critical P = 0.015), every 5 mmol/L increase in homocysteine levels showed a maximum brain volume reduction of 4.4%, relative to the MDT. In addition, after correcting for multiple statistical comparisons (FDR, q = 0.05, critical uncorrected P = 0.004), every 5 mmol/L increase in homocysteine levels showed an association with brain volume changes in the MCI subjects, with a maximum brain volume deficit of 7.5% relative to the mean template.



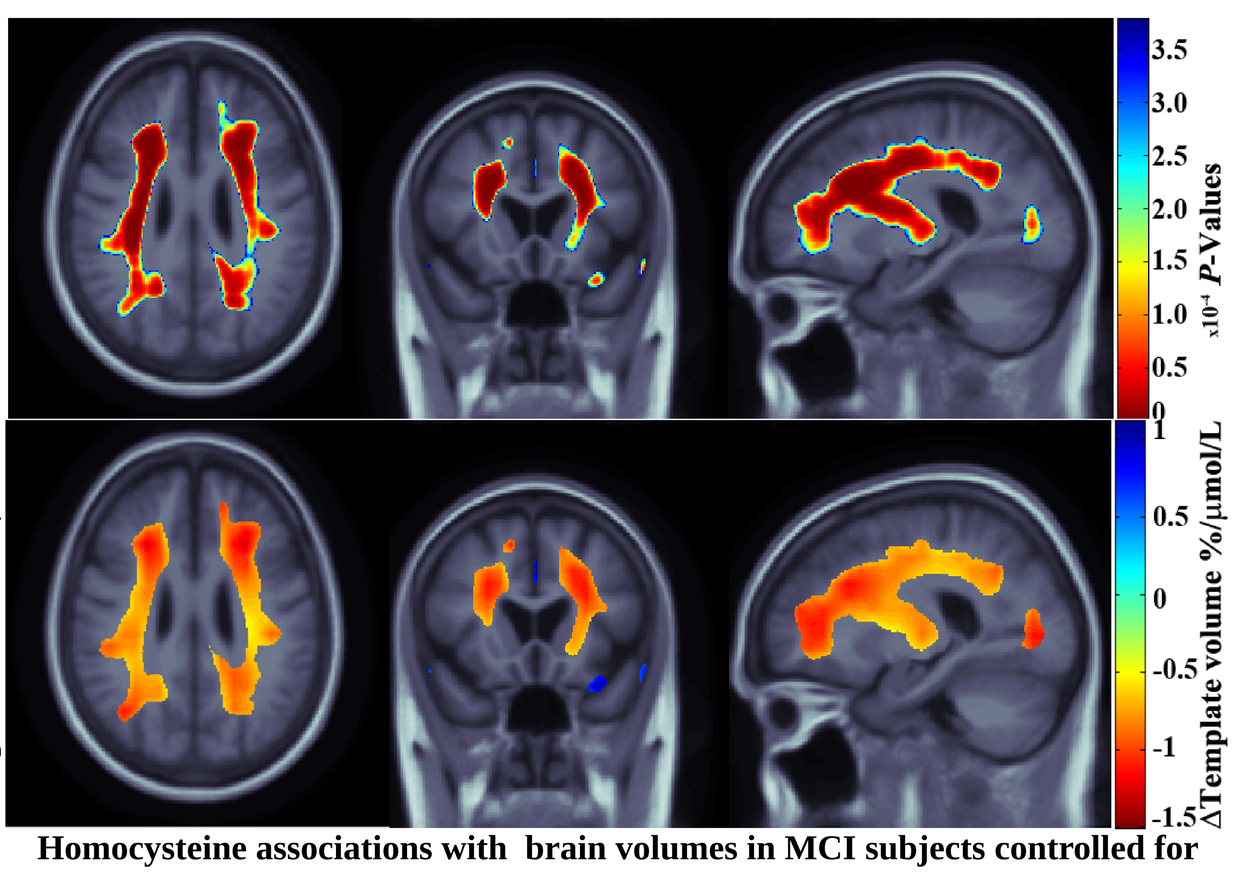
The mean total plasma homocysteine levels are 10.8+/-3.3, 10.6+/-2.8, and 10.0+/-2.9 μmol/L for the AD, MCI and control groups respectively. Homocysteine levels in the healthy controls were significantly lower when compared to subjects with AD and MCI.

CONCLUSION

Automated whole brain volumetric analysis of brain MRI revealed a three-dimensional pattern of homocysteine-associated brain differences. Hyperhomocysteinemia may promote the magnitude of atrophy in the brain. These statistical associations may help in understanding how neurodegenerative disorders develop.



Homocysteine associations with brain volumes in all ADNI subjects controlled for age, sex and diagnosis Upper–*p*-maps, Lower-betamaps (Left side of picture=right side of brain)



Homocysteine associations with brain volumes in MCI subjects controlled for age,and sex