Neuroimaging correlates of white matter hyperintensity burden and *MTHFR* gene in relation to beta-amyloid in healthy elderly

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Purpose

Small vessel ischemic changes in the brain white matter are visualized as hyperintense signal abnormalities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences of the brain and are referred to as white matter hyperintensities (WMH). These are commonly associated with senescence. However, neurovasacular inflammatory markers such as homocysteine can increase the risk for WMH.

Beta-amyloid deposition in the brain is implicated in a cascade of events leading to pathogenesis of AD. Homocysteine, associated with Alzheimer's disease (AD) accelerates brain atrophy (Yoshita et al. 2006, Smith et al. 2008, Rajagopalan et al. 2011), particularly in the presence of beta-amyloid deposition (Provenzano et al. 2013).

WMH has high heritability estimates and yet no genetic polymorphism has consistently shown to affect it. *MTHFR* is a candidate gene for elevated plasma homocysteine levels and is implicated in AD and brain atrophy. However, prior studies, including ours studying WMH in relation to *MTHFR* have found the association to be inconsistent. (Kohara et al. 2003, Rajagopalan et al. 2012).

In order to understand the underlying pathways determining associations between WMH and *MTHFR*, and identify potential novel pathways, we postulated interactions between *MTHFR* and cerebral amyloid deposition in determining WMH burden.

Methods

MTHFR (rs1801133) alleles were genotyped in 303 cognitively normal elderly subjects (72.2 +/- 0.3 yrs) enrolled in the Alzheimer's Disease Neuroimaging Initiative GO/2 study (http://adni.loni.usc.edu). WMH volumes were computed from 2D FLAIR images at University of California (UC), Davis and downloaded for further analysis. Beta-amyloid positivity was estimated using cerebral amyloid

deposition demonstrated on [^{18}F]Florbetapir PET scans processed at UC, Berkeley (Landau et al. 2013) and Beta-amyloid measured in cerebrospinal fluid.

Results

Increased WMH volume was noted in healthy cognitively normal elderly who carried the T allele of the *MTHFR* gene and also has cerebral beta-amyloid deposition. Risk gene carriers without beta-amyloid deposition did not show significant association with WMH. An interaction term denoting carrying *MTHFR* gene polymorphism and having cerebral beta-amyloid deposition further increased WMH burden. All associations were controlled for age, sex and ApoEe4 status.

Conclusions

We have shown that cognitively normal elderly who carry *MTHFR* gene mutation and are at increased risk for homocysteine, show increased WMH, if they have concurrent beta-amyloid deposition in their brain. Potential synergistic interactions between carrying the *MTHFR* gene and beta-amyloid may affect the WMH burden. Future neuroimaging studies mapping amyloid and WMH, in relation to *MTHFR*, may offer new insights into novel AD-related pathways.

Figure 1: Background (solid arrows) and postulated hypothesis (dashed arrows).

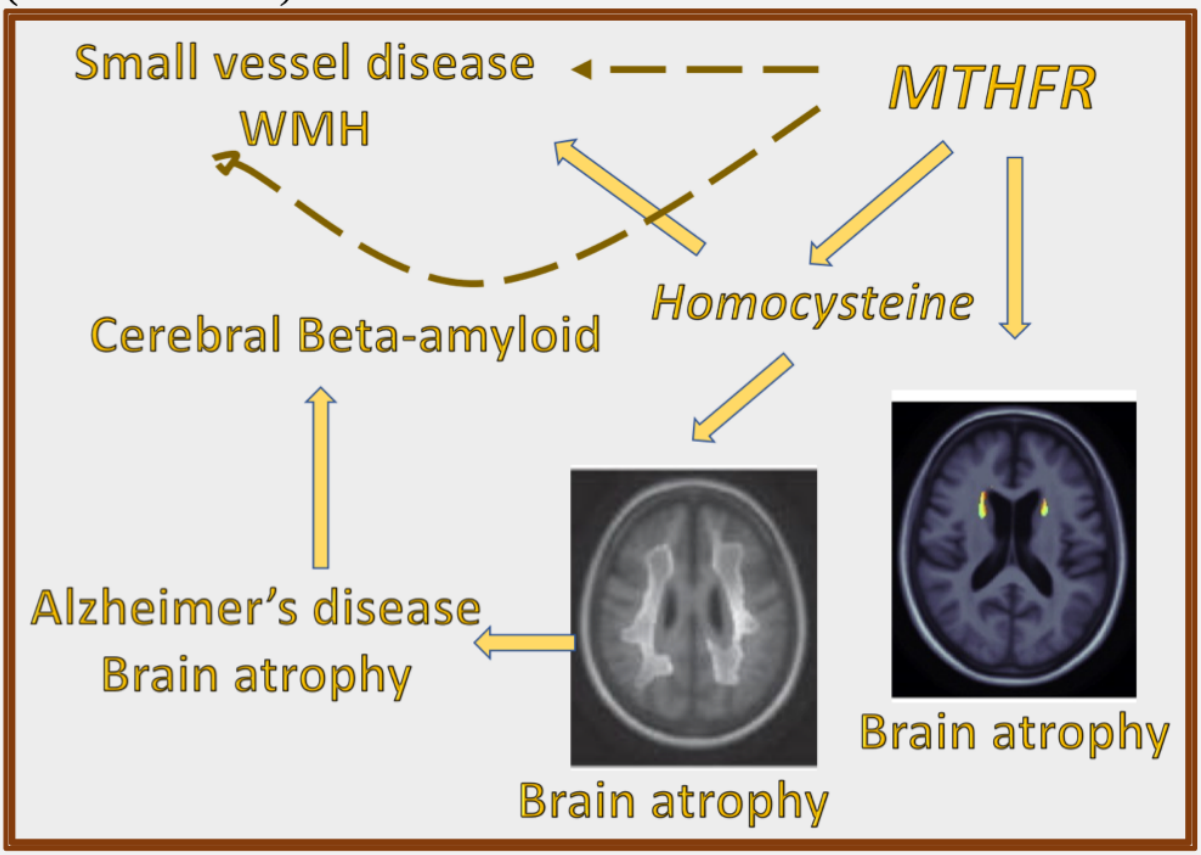

Figure 2: Results for association of WMH with *MTHFR* in relation to cerebral amyloid deposition.

WMH		Beta-value	P-value	N
MTHFR	in Abeta_Positive	4.03	0.006*	158
MTHFR	in Abeta_Negative	-0.56	0.151	136
Abeta_Positive		2.64	0.016*	303
Interaction *MTHFR* *Abeta		4.66	0.003*	294

References:

Kohara, K., M. Fujisawa, F. Ando, Y. Tabara, N. Niino, T. Miki and H. Shimokata (2003). "MTHFR gene polymorphism as a risk factor for silent brain infarcts and white matter lesions in the japanese general population." Stroke 34(5): 1130-1135.

Provenzano, F. A., J. Muraskin, G. Tosto, A. Narkhede, B. T. Wasserman, E. Y. Griffith, V. A. Guzman, I. B. Meier, M. E. Zimmerman and A. M. Brickman (2013). "White matter

hyperintensities and cerebral amyloidosis: necessary and sufficient for clinical expression of Alzheimer disease?" JAMA neurology 70(4): 455-461.
Rajagopalan P, Hua X, Toga AW, Jack CR Jr, Weiner MW, Thompson PM (2011). “Homocysteine effects on brain volumes mapped in 732 elderly individuals.“ Neuroreport. Jun 11; 22(8):391-5.
Rajagopalan, P., N. Jahanshad, J. L. Stein, X. Hua, S. K. Madsen, O. Kohannim, D. P. Hibar, A. W. Toga, C. R. Jack and A. J. Saykin (2012). "Common folate gene variant, MTHFR C677T, is associated with brain structure in two independent cohorts of people with mild cognitive impairment." NeuroImage: Clinical 1(1): 179-187.
Smith, E. E., S. Egorova, D. Blacker, R. J. Killiany, A. Muzikansky, B. C. Dickerson, R. E. Tanzi, M. S. Albert, S. M. Greenberg and C. R. Guttmann (2008). "Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia." Archives of neurology 65(1): 94-100.
Yoshita, M., E. Fletcher, D. Harvey, M. Ortega, O. Martinez, D. Mungas, B. Reed and C. DeCarli (2006). "Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD." Neurology 67(12): 2192-2198.