commentary³) used a photothrombotic model in mice to demonstrate that soluble TM administered after stable thrombotic occlusion of the middle cerebral artery restored blood flow and reduced infarct volume without increasing hemorrhage. In another study, Ryang et al.⁴ confirmed the efficacy and safety of soluble TM in a transient middle cerebral artery occlusion model in rats. We believe that these observations together with those discussed by Fisher should—as indicated by Fisher—“awaken interest in TM by stroke neurologists” and “may help generate attention for a clinical trial of this compound in acute ischemic stroke.”

Copyright © 2012 by AAN Enterprises, Inc.

1. Fisher M. Thrombomodulin and the brain: past, present, and future. *Neurology* 2012;78:157–158.
2. Giwa MO, Williams J, Elderfield K, et al. Neuropathologic evidence of endothelial changes in cerebral small vessel disease. *Neurology* 2012;78:167–174.
3. Su EJ, Geyer M, Wahl M, et al. The thrombomodulin analog Solulin promotes reperfusion and reduces infarct volume in a thrombotic stroke model. *J Thromb Haemost* 2011;9:1174–1182.
4. Ryang YM, Dang J, Kipp M, et al. Solulin reduces infarct volume and regulates gene-expression in transient middle cerebral artery occlusion in rats. *BMC Neurosci* 2011;12:113.
5. Andreou AP, Crawley JT. Thrombomodulin analogues for the treatment of ischemic stroke. *J Thromb Haemost* 2011;9:1171–1173.

NUTRIENT BIOMARKER PATTERNS, COGNITIVE FUNCTION, AND MRI MEASURES OF BRAIN AGING

Cedric Annweiler, Angers, France; Manuel Montero-Odasso, Robert Bartha, London, Canada; Olivier Beauchet, Angers, France: Recently, Bowman et al.¹ reported that a plasma nutrient pattern rich in vitamin D was associated with better cognition and larger brain volume on MRI in older community dwellers. Despite comprehensively estimating nutrients, such studies could be enhanced by measuring regional volumes rather than whole-brain volume to identify specific brain areas protected by vitamins. Since structural brain changes manifest long before cognitive symptoms, accurate morphometric approaches are crucial.² Current automated segmentation algorithms can determine the volume of different regions of interest,³ which may help to clarify vitamins' effects. However, restricting the scope of investigations limits the relevance of findings. An alternative is the measurement of lateral ventricle volume, which is an indirect measure of multipoint atrophy because CSF is under pressure and any parenchymal loss results in passive ventricle expansion.⁴ Modern software can segment ventricles in subvol-

umes, providing insight into the volume of adjacent brain structures. For instance, atrophy of medial temporal lobe leads to ventricle temporal horn enlargement, and expansion of ventricle frontal horn reflects frontal lobe shrinkage.⁵ Future studies should describe regional changes in brain, ventricles, or both to better understand the neurobiological basis of cognitive changes associated with diet, and specifically with the remarkable neurosteroid vitamin D.

Author Response: Gene L. Bowman, Lisa Silbert, Hiroko Dodge, Joseph Quinn, Jeffrey Kaye, Portland, OR: We thank Annweiler et al. for their comments. In this first analysis investigating nutrient biomarker profiles in relation to brain health,¹ we started from the generalizable premise that there would be a distinct nutrient combination associated with brain health marked by well-established global volumetric indices. There are data demonstrating that overall brain atrophy is a measure of age-related brain health, risk for disease, or reserve.^{6,7} Essentially all regions of the brain atrophy with healthy aging⁷; total brain volume is a global index of the magnitude of this phenomenon. Similarly, white matter change has been associated with vascular disease and thus this MRI marker (total white matter hyperintensity volume) would suggest nutrient profiles associated with protection from global vascular disease.

We considered it premature to generate a hypothesis related to specific subregions; there is no a priori reason to expect that the left dorsal medial fasciculus Y is associated with vitamin Z. Practically speaking, we had to resist the temptation to parcel the brain into potentially hundreds of subregions to avoid type II errors. We have subsequently evaluated total ventricular volume (another marker of overall atrophy) and the result is consistent with the use of total brain volume as a marker.

Future studies will address more specific regions guided by this preliminary data. We appreciate the value of using ventricular subregions as ready surrogates for more targeted studies such as of the medial temporal lobe.⁸

Copyright © 2012 by AAN Enterprises, Inc.

1. Bowman GL, Silbert LC, Howieson D, et al. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. *Neurology* 2012;78:241–249.
2. Dickerson BC, Stoub TR, Shah RC, et al. Alzheimer-signature MRI biomarkers predicts AD dementia in cognitively normal adults. *Neurology* 2011;76:1395–1402.
3. Pham DL, Xu C, Prince JL. Current methods in medical image segmentation. *Annu Rev Biomed Eng* 2000;2:315–337.
4. Bradley WG, Orrison WW. Hydrocephalus and cerebrospinal fluid flow. In: Orrison WW, ed. *Neuroimaging*. Philadelphia: Saunders; 2000:1704–1716.

5. Chance SA, Esiri MM, Crow TJ. Ventricular enlargement in schizophrenia: a primary change in the temporal lobe? *Schizophr Res* 2003;62:123–131.
6. Jack CR, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology* 2004;62:591–600.
7. Fjell AM, Walhovd KB, Fennema-Notestine C, et al. One-year brain atrophy evident in healthy aging. *J Neurosci* 2009;29:15233–15231.
8. Erten-Lyons D, Howieson D, Moore MM, et al. Brain volume loss in MCI predicts dementia. *Neurology* 2006;66:233–235.

Neurology®

Nutrient Biomarker Patterns, Cognitive Function, and Mri Measures of Brain Aging

Cedric Annweiler, Gene L. Bowman, Manuel Montero-Odasso, et al.

Neurology 2012;78;1281-1282

DOI 10.1212/01.wnl.0000414241.41860.13

This information is current as of April 16, 2012

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/78/16/1281.full>

References

This article cites 7 articles, 4 of which you can access for free at:
<http://n.neurology.org/content/78/16/1281.full#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright Copyright © 2012 by AAN Enterprises, Inc.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.