Conserved Patterns of White Matter Hyperintensity Distribution in Alzheimer's, Cerebral Amyloid Angiopathy, and Healthy Aging

C. M. Holland[1,2], E. E. Smith[3], I. Csapo[1], M. E. Gurol[3], D. A. Brylka[1], C. R. Guttmann[1], and S. M. Greenberg[3]

[1]Center for Neurological Imaging and the Department of Radiology, Brigham and Women's Hospital, Boston, MA, United States, [2]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, United States, [3]Neurology Clinical Trials Unit and Department of Neurology, Massachusetts General Hospital, Boston, MA, United States

Introduction: White matter hyperintensities (WMH), as detected on T2-weighted magnetic resonance imaging (MRI), are present in many neurological diseases and are frequent in healthy aged individuals as well[1]. In Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA), subjects have greater global WMH burdens compared to non-demented, healthy aged (HA) subjects[2]]. In this retrospective analysis, we examined the spatial distributions of MRI-detected white matter lesions in patients with CAA, AD/MCI, and HA subjects. These spatial distributions were compared statistically to determine regions of significant difference. Further, an atlas of normal cerebral perfusion patterns was used to examine these distributions in the context of regional perfusion differences. The relationship between lesion size and normal regional perfusion was also examined.

Methods: Subjects with a diagnosis of CAA (n=32) or AD/MCI (n=41), and non-demented, HA individuals (n=29) were included in our study. All subjects underwent magnetic resonance imaging (MRI) examination of the brain at 1.5 Tesla. WMH was segmented from T2-weighted (T2 and FLAIR) MRI images using a semi-automated method described previously[2, 3]. Regions of intracranial hemorrhage (ICH) were also segmented and excluded from spatial analyses. In CAA subjects with ICH, total WMH volume was estimated by doubling the WMH volume of the uninvolved hemisphere[2]. WMH volumes were calculated in common space to account for global differences in head size. WMH frequency maps from the HA, AD/MCI, and CAA cohorts were calculated and compared using voxelwise logistic regression with and without controlling for total WMH volume.

An atlas of normal cerebral perfusion was calculated from single photon emission tomography (SPECT) images acquired from 47 healthy individuals between the ages of 22 and 49 (mean 34.3 ± 7.6, 53.2% male) and used to analyze the distribution of WMH in the context of regional perfusion patterns. Subject images and segmentations were registered into the ICBM452 coordinate space using affine transformation (FLIRT, Analysis Group, FMRIB Oxford, UK)[4, 5]. The SPECT perfusion atlas was re-sampled into the native space of each individual subject by applying the inverse transformation from the structural image to ICBM registrations. Atlas perfusion values co-localized with WMH were compared among our three cohorts and the relationship between lesions frequency and perfusion was also examined.

Results: Total WMH volume was significantly lower in the HA cohort as compared to both the AD/MCI and CAA groups ($p < 0.001$ and $p < 0.0001$; respectively), but did not differ between the AD/MCI and CAA groups ($p = 0.19$). The distribution of WMH appears similar in all three groups, with almost all regions of WMH in the HA cohort present also in the AD/MCI and CAA subjects, albeit at relatively higher frequency due to the greater total WMH burden in the disease cohorts (Figure 1). Voxelwise logistic regression revealed some regions of significant difference between both disease groups as compared to the HA cohort, however these differences were lost when the analysis was controlled for total WMH volume.

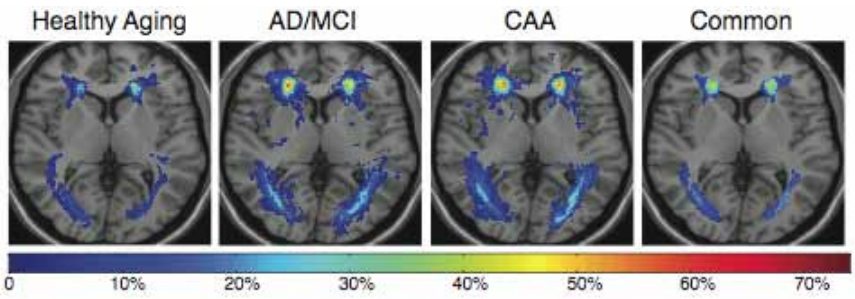

Figure 1: Spatial Distribution of WMH. An exemplary slice from the WMH frequency distributions for each of our subject groups overlain on the ICBM452 template, as well as a mask of the regions of WMH common to all 3 groups and the cumulative population WMH frequency in these regions.

Normal perfusion values for regions in which WMH were detected were significantly lower in the HA group both versus AD/MCI ($p < 0.0001$) and CAA ($p < 0.0001$). However these differences were accounted for by the larger volumes of WMH unique to either of the disease cohorts, which occured in white matter regions of higher relative perfusion values. WMH common to all three groups tended to be present in regions of lower relative normal perfusion. The distribution of WMH volume with respect to normal perfusion patterns is presented in Figure 2 and reflects not only the volumetric differences, but also the increased prevalence of WMH in regions of higher relative perfusion in the AD/MCI and CAA groups. The frequency of WMH in a given voxel and the normal perfusion value in that region had a strong negative correlation for all subjects ($r = - 0.54$, $p < 0.0001$) and within all subgroups, thus illustrating that WMH are more frequent in regions of the cerebral white matter with lower relative perfusion.

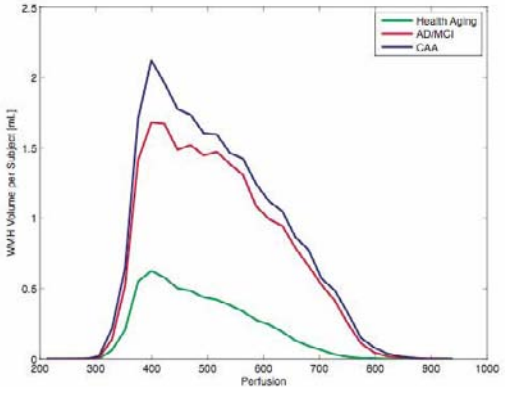

Figure 2: Histogram of WMH Volumes (ml/subject) by normal regional perfusion values as defined by our SPECT atlas.

Discussion: This work sought to compare the spatial distribution of WMH, an MRI surrogate of white matter damage, in two disease groups to that observed in healthy aging. While Alzheimer's disease and CAA are associated with a greater burden, we have shown that when controlling for these differences in total WMH volumes the patterns of spatial distribution are not significantly different. This conserved pattern of WMH in the context of what may be distinct pathogenetic mechanisms, may be due to common susceptibility of the white matter in these regions or alternatively may be due to differential repair capacity both of which could possibly be modulated by the lower relative perfusion present in the periventricular white matter. The role of perfusion in either the occurrence of persistence of WMH is further supported by the strong inverse correlation between WMH frequency and regional perfusion values.

References:

1. Meyer, J.S., J. Kawamura, and Y. Terayama, *White matter lesions in the elderly.* J Neurol Sci, 1992. **110**(1-2): p. 1-7.
2. Gurol, M.E., et al., *Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy.* Neurology, 2006. **66**(1): p. 23-9.
3. Chen, Y.W., et al., *Progression of white matter lesions and hemorrhages in cerebral amyloid angiopathy.* Neurology, 2006. **67**(1): p. 83-7.
4. Jenkinson, M. and S. Smith, *A global optimisation method for robust affine registration of brain images.* Med Image Anal, 2001. **5**(2): p. 143-56.
5. Smith, S.M., et al., *Advances in functional and structural MR image analysis and implementation as FSL.* Neuroimage, 2004. **23 Suppl 1**: p. S208-19.

Acknowledgement: This work was supported in part by the NINDS/NIH F30-NS049808 and the Harvard Center for Neurodegeneration & Repair