Controlling for white matter hyperintensities in cross-sectional voxel-wise diffusion MRI studies of aging

C. M. Barth[1], D. A. Bennett[2], and K. Arfanakis[1]

[1]*Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, Illinois, United States,* [2]*Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, United States*

Target Audience: Researchers using diffusion MR imaging in aging

Purpose: Brain white matter hyperintense lesions (WMHs) are common in older adults [1]. WMHs are best visualized in T2-weighted FLAIR images, but they also affect image intensities in different types of MR contrast, including diffusion measurements. When diffusion imaging is used to investigate the microstructure of brain tissue in cross-sectional voxel-wise studies of aging, and WMHs are not the target of the investigation, it is necessary to control for the effects of WMHs on the diffusion parameters. This is often accomplished by including as a covariate in statistical models a quantitative or semi-quantitative measure of the total volume of WMHs over the whole brain [2,3]. However, this approach may be problematic for model fitting since: a) it controls for the total volume of WMHs in all voxels, even in those that do not contain WMHs, and b) in voxels that do contain WMHs, the effect of the underlying pathology on the diffusion characteristics may be independent of the total volume of WMHs. An alternative approach for controlling for WMHs in cross-sectional voxel-wise diffusion imaging analyses in aging research is to use knowledge about the location of WMHs in the brain, and control for a binary parameter describing the presence or absence of WMHs in different voxels (i.e. control for the mask of WMHs) [4]. The purpose of this study was to test the hypothesis that controlling for the mask of WMHs, improves model fitting and allows more sensitive detection of other microstructural abnormalities compared to controlling for the total volume of WMHs.

Methods: A community-dwelling cohort of older adults (N=368) (82 ± 7 years of age) participating in the Rush Memory and Aging Project was included in this study [5]. T1-weighted MPRAGE, T2-weighted FLAIR and SE-EPI-DTI data were collected using a 1.5 Tesla MRI scanner. WMHs were automatically segmented using a support vector machine based on signals from both the MPRAGE and FLAIR sequences. For the DTI data, corrections for bulk motion and distortions due to eddy-currents and field non-uniformities, B-matrix reorientation, and diffusion tensor calculation, were conducted using TORTOISE [6]. Fractional anisotropy (FA) values were calculated in each voxel. Tract-Based Spatial Statistics (TBSS) [7] was then used to project FA information from all subjects to a reference white matter skeleton [8]. Projection parameters were stored for each participant. Two groups of 30 participants each were then randomly selected from the original cohort. Microstructural changes were simulated in one of the two groups, in all brain voxels, by increasing the secondary and tertiary eigenvalues of the diffusion tensor by 3%. The altered FA values were recalculated and were re-projected onto the skeleton using the stored projection parameters. FA values along the skeleton were then compared across the two groups, controlling for age, sex, level of education, and total volume of WMHs (approach #1) or the mask of WMHs (approach #2). The null distribution was generated using the randomise tool and 1000 permutations. Differences were considered significant at $p<0.05$, Family Wise Error corrected. Threshold-Free Cluster Enhancement was used to define significant clusters. The random selection of two groups and simulation of whole brain abnormalities was repeated 300 times. The percentage of times a significant FA difference was detected was compared in each voxel across the two methods for controlling for WMHs.

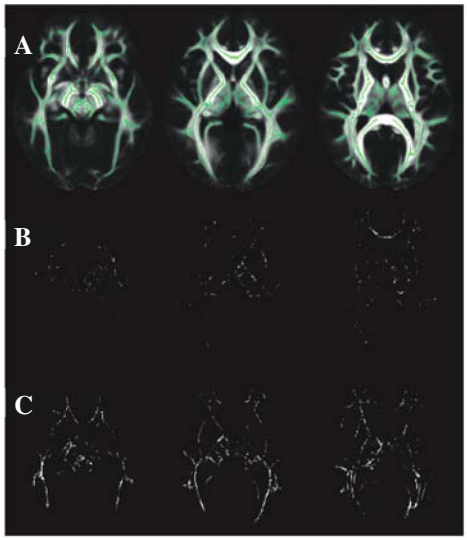

Figure 1. A) FA reference (grayscale) and corresponding white matter skeleton (green) used in this work. B) Map of the difference in the percentage of successfully detected simulated abnormality in voxels where approach #1 for controlling for WMHs detected more abnormalities than approach #2. C) Map of the difference in the percentage of successfully detected simulated abnormality in voxels where approach #2 for controlling for WMHs detected more abnormalities than approach #1. Approach #2 detected more simulated abnormalities and in more voxels of the skeleton than approach #1.

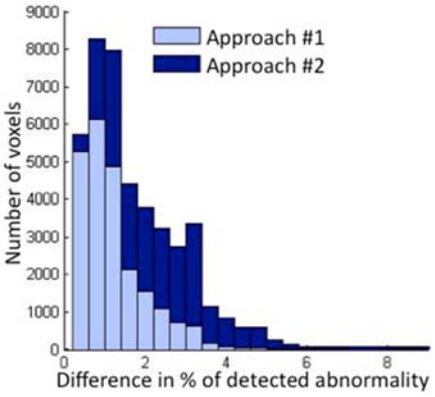

Figure 2. Histograms of the number of voxels with a higher percentage of successfully detected simulated abnormality when using approach #1 (light blue) and when using approach #2 (dark blue), as a function of that difference between approaches. Approach #2 detected more simulated abnormalities and in more voxels of the skeleton than approach #1.

Results & Discussion: It was demonstrated that controlling for the mask of WMHs (approach #2) allowed detection of simulated abnormalities more often and in more voxels than controlling for the total volume of WMHs (approach #1) (Figs. 1 & 2). Therefore, the proposed approach for controlling for WMHs is preferable over the conventional approach. This finding is crucial for a number of diffusion imaging studies of aging, since WMHs are very common in the brain of older adults and controlling for them is necessary.

References: [1] Erten-Lyons D, et al. *Neurology* 2013;81:977-983. [2] Wersching H, et al. *Neurology* 2010;74:1022-1029. [3] Miralbell J, et al. *Neurobiol Aging* 2012;33:1003.e9-e17. [4] Arfanakis K, et al. *PLoS One* 2013;8:e73107. [5] Bennett DA, et al. *Curr Alzheimer Res* 2012;9:646–663. [6] Pierpaoli C, et al. *ISMRM* 2010, p.1597. [7] Smith SM, et al. *Neuroimage* 2006;31:1487–1505. [8] Zhang S, et al. Neuroimage 2011;54:974-984.