Neuropathologic correlates of brain white matter hyperintensity volume measured with ex-vivo MRI.

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Target Audience: Researchers in MRI of Alzheimer's disease and aging.

Purpose:

White matter lesions appearing hyperintense (WMH) on T2-weighted MR images are common in the elderly. WMHs are thought to be secondary to small vessel ischemic changes and have been associated with reduced cognition and increased risk of dementia, including Alzheimer's disease [1]. The purpose of this study was to investigate the link between the total volume of WMHs and various age-related neuropathologies in a large community cohort.

Methods:

Cerebral hemispheres were obtained from 246 deceased participants of the Rush Memory and Aging Project [2] and the Religious Orders Study [3], two longitudinal, epidemiologic clinical-pathologic cohort studies of aging. All hemispheres were imaged ex-vivo, while immersed in 4% formaldehyde solution, using a 2D fast spin-echo sequence (FSE) with multiple echo-times and a FLAIR sequence on a 3T clinical MRI scanner. Details about the tissue handling and ex-vivo imaging protocols can be found in [4]. An experienced observer blinded to all pathologic and clinical data outlined WMHs on multi-echo FSE images from TE = 50 msec, using FLAIR images for guidance. Neuropathologic assessment was performed by a board-certified neuropathologist blinded to all clinical and imaging findings [5]. The pathologies that were considered in analyses were: neurofibrillary tangles, amyloid plaques, gross and microscopic chronic infarcts. A composite measure of global AD pathology was created from counts of neurofibrillary tangles, neuritic and diffuse plaques [6]. Multiple linear regression was used to investigate the link between total WMH volume measured ex-vivo and age-related neuropathologies, controlling for age at death, sex, education, height, postmortem interval to fixation and to imaging.

N	246
Age at death, y (SD)	90.2 (6.4)
Gross Infarcts, n (%)	87 (35.4)
Microscopic Infarcts, n (%)	70 (28.5)
AD-pathology, n (%)	
-High likelihood	51 (21.7%)
-Intermediate likelihood	119 (48.4%)

Results:

It was demonstrated that the total WMH volume was significantly associated with the summary measure of AD pathology (p=0.003) and gross chronic infarcts (p=0.0007).

Discussion & Conclusion:

The results of this study offer support to the hypotheses that WMHs may result from Wallerian degeneration secondary to neurodegenerative changes [7,8], or from ischemia leading to both vascular injury and neurodegenerative changes of AD [1,8,9]. To our knowledge, this study is the largest MRI-pathology investigation of WMHs in a community cohort to date. This is an ongoing study. Additional neuropathologies are currently being considered.

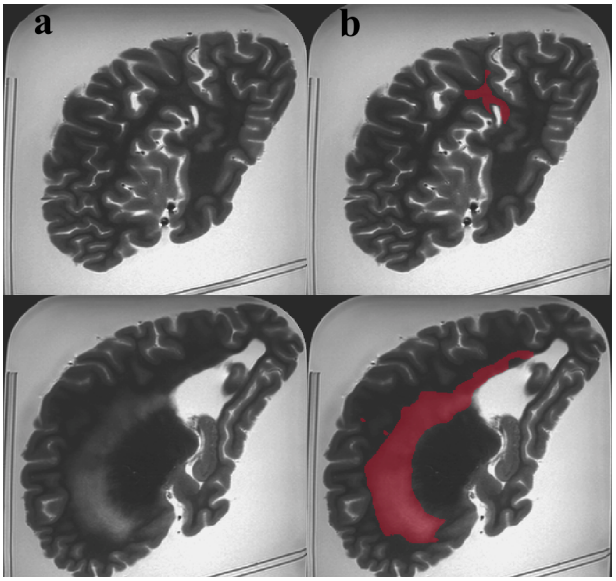

Figure: Examples of (a) raw ex-vivo T2-weighted images from a single brain hemisphere and (b) corresponding regions of WMHs in red.

References: [1] Erten-Lyons D, et al. *Neurology* 2013;81:977-983. [2] Bennett DA, et al. *Curr Alzheimer Res* 2012;9:646–663. [3] Bennett DA, et al. *J Alzheimers Dis* 2013;33 Suppl 1:S397-403. [4] Kotrotsou A, et al. *Magn Reson Med* doi: 10.1002/mrm.24661. [5] Schneider JA, et al. *Neurology* 2007;69:2197-2204. [6] Bennett DA, et al. *Lancet Neurol* 2006;5:406-412. [7] Bozzali M, et al. *J Neurol Neurosurg Psychiatry* 2002;72:742-746. [8] Polvikoski TM, et al. *Neurology* 2010;75:2071-2078. [9] Zlokovic BV. *Nat Rev Neurosci* 2011;12:723-738.