Ex-vivo brain MR morphometric-pathologic investigation in a community cohort of older adults.

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Target Audience: Researchers in MRI of Alzheimer's disease and other age-related neuropathologies.

Purpose: Alzheimer's disease (AD) pathology commonly coexists with other age-related neuropathologies in the brain of older persons [1]. Although brain atrophy is considered a biomarker of AD pathology, other neuropathologies may also lead to brain atrophy. Most of the age-related neuropathologies can only be diagnosed histologically, however, only a handful of studies have combined brain MR volumetry/morphometry with measures of neuropathology obtained after death [2], and those studies suffer from low numbers of participants, relatively long periods between imaging and death, and low level of detail in terms of the spatial patterns of brain atrophy. Thus, the relation between brain atrophy and age-related neuropathology is not well-established. Ex-vivo brain MRI overcomes several of the obstacles that complicate MRI-pathology investigations and can provide measurements of brain structural characteristics that are linked to those collected in-vivo [3]. Therefore, the purpose of this investigation was to assess the neuropathologic correlates of brain macrostructure by combining ex-vivo MRI regional analysis of volumes examined in normalized space (RAVENS) [4] and pathology information on a large community cohort of older persons.

Methods: Cerebral hemispheres were obtained from 195 deceased participants of the Rush Memory and Aging Project [5] and the Religious Orders Study [6], two longitudinal, epidemiologic clinical-pathologic cohort studies of aging. Participants had a mean age at death of 89.4 years (SD=6.1), a mean of 15.8 years of education (SD=3.9), 72% were women, 29% had no cognitive impairment, 21% were diagnosed with mild cognitive impairment and 50% with probable AD at the time of death. All hemispheres were imaged ex-vivo, while immersed in 4% formaldehyde solution, using a 2D fast spin-echo sequence with multiple echo-times (TEs) on a clinical 3T MRI scanner [3]. Signals from fluid were removed from all image volumes, and gray and white matter were segmented using in-house software. The image volumes from all participants were also registered to a reference using deformable registration via attribute matching and mutual-saliency weighting (DRAMMS) [7]. The resulting deformation fields were applied to the corresponding gray and white matter masks, generating RAVENS maps. The RAVENS maps were normalized by the height of the participants and smoothed with a 5 mm Gaussian kernel. Following ex-vivo MRI, hemispheres underwent neuropathologic assessment. The pathologies that were considered in analyses were: neurofibrillary tangles, amyloid plaques, hippocampal sclerosis, transactive response DNA-binding protein 43 (TDP43), Lewy bodies, gross and microscopic chronic infarcts, and cerebral amyloid angiopathy [1]. The general linear model was used to investigate the association of RAVENS values in gray and white matter with age-related neuropathologies, controlling for age at death, sex, education, postmortem interval to fixation and to imaging. The null distribution was built using the "randomize" tool in FSL (FMRIB, University of Oxford, UK) and 5000 permutations of the data. Differences were considered significant at $p<0.05$, Family Wise Error corrected.

Results: Significant negative correlation was detected between RAVENS values in a number of gray and white matter regions and the measures of AD pathology and hippocampal sclerosis ($p<0.05$, FWE-corrected) (Fig.1). Only gray matter results are shown in Figure 1 due to space limitations. No other pathologies considered here showed significant correlations with RAVENS values.

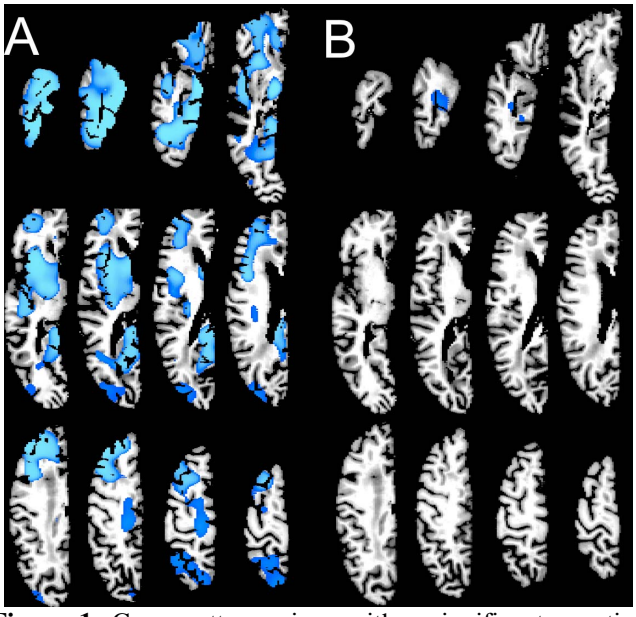

Figure 1. Gray matter regions with a significant negative correlation between RAVENS values and (A) AD pathology, and (B) hippocampal sclerosis ($p<0.05$, FWE-corrected).

Discussion and Conclusion: To our knowledge, this study is the largest MR morphometric-pathologic investigation in a community cohort to date [2]. Consequently, the present study provides the most detailed information currently available on the spatial patterns of brain atrophy associated with age-related neuropathologies. The findings of this work offer support to literature on the effects of AD pathology [8] and hippocampal sclerosis [9]. This is an ongoing investigation with a growing number of participants.

References: [1] Schneider JA, et al. *Neurology* 2007;69:2197-2204. [2] Erten-Lyons D, et al. *JAMA Neurol* 2013;70:616-622. [3] Kotrotsou A, et al. *Magn Reson Med* 2014;71:364-374. [4] Davatzikos C, et al. *Neuroimage* 2001;14:1361-1369. [5] Bennett DA, et al. *Curr Alzheimer Res* 2012;9:646–663. [6] Bennett DA, et al. *J Alzheimers Dis* 2013;33 Suppl 1:S397-403. [7] Ou Y, et al. *Med Image Anal* 2011;15:622–639. [8] Bakkour A, et al. *Neurology* 2009;72:1048-1055. [9] Nelson PT, et al. *Acta Neuropathol* 2013;126:161-177.