Neuropathologic correlates of regional brain volumes assessed with ex-vivo MRI.

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

Purpose: Brain atrophy is considered a biomarker of Alzheimer's disease (AD) pathology in clinical trials and biomarker studies. However, AD pathology in the elderly commonly coexists with other neuropathologies that may also lead to atrophy [1], and only a handful of studies have combined brain MR volumetry with measures of neuropathology obtained after death [2]. Furthermore, published structural MRI-pathology investigations 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 volumetric measurements that are linked to those collected in-vivo [3]. Therefore, the purpose of this investigation was to assess the neuropathologic correlates of regional brain volumes by combining ex-vivo MR volumetry and pathology information on a large community cohort of older persons.

N	166
Age at death, yr	89.6 ± 6.3
Males, n (%)	49 (30%)
Educational level, yr	15.9 ± 3.8
Clinical Diagnosis	
-Mild cognitive impairment	31 (19%)
-Probable AD	83 (50%)
Postmortem Interval to Fixation, h	8.3 ± 5.3
Postmortem Interval to Imaging, d	50 ± 23
NIA Reagan (AD pathology) (%)	
-High	35 (21%)
-Intermediate	80 (48%)
Cerebral Amyloid Angiopathy	
-Mild to moderate	104 (63%)
-Severe to very severe	31 (19%)
Gross Chronic Infarcts	60 (36%)
Microscopic Chronic Infarcts	45 (27%)
Hippocampal Sclerosis (%)	21 (13%)

Methods: Cerebral hemispheres were obtained from 166 deceased participants of the Rush Memory and Aging Project [4] and the Religious Orders Study [5], two longitudinal, epidemiologic clinical-pathologic cohort studies of aging. Demographic, clinical and neuropathologic information is included in the Table. 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 3T clinical MRI scanner [3]. A multi-atlas approach was used to segment ex-vivo brain MRI data into white and gray matter, and gray matter into 34 cortical and 8 subcortical regions [3]. All volumes were normalized by the height of the participants. Following ex-vivo MRI, hemispheres underwent neuropathologic assessment. The pathologies that were considered in analyses were: neurofibrillary tangles, amyloid plaques, Lewy bodies, hippocampal sclerosis, gross and microscopic chronic infarcts, and cerebral amyloid angiopathy [1]. A composite measure of global AD pathology was created from counts of neurofibrillary tangles, neuritic and diffuse plaques. Multiple linear regression was used to investigate the link between the volume of each segmented brain region and age-related neuropathologies, controlling for age at death, sex, education, postmortem interval to fixation and to imaging. Correction for multiple comparisons was performed using the False Discovery Rate (FDR) procedure. Statistical significance was set at $p<0.05$.

Results: Figure 1 shows brain regions with a significant negative association between their volume and the summary measure of AD pathology ($p<0.05$, FDR-corrected). A significant negative correlation was also shown between the volume of the hippocampus, entorhinal cortex, temporal pole, and superior frontal gyrus and hippocampal sclerosis ($p<0.05$, FDR-corrected) (figure not shown due to space limitations). No other pathologies considered here showed significant correlations with the volume of the segmented regions.

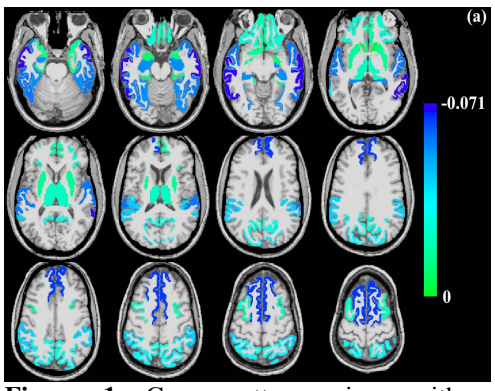

Figure 1. Gray matter regions with a significant negative association between their height-corrected volume measured ex-vivo and AD pathology ($p<0.05$, FDR-corrected) (model estimates are in units: 10^{-5} mm^2). The volume of white matter also showed a significant negative association with AD pathology, but is not shown here to improve visualization.

Discussion and Conclusion: To our knowledge, this study is the largest MR volumetric-pathologic investigation in a community cohort to date, and the only MR volumetric-pathologic investigation assessing a high number of brain regions [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 [6] and hippocampal sclerosis [7]. 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* doi: 10.1002/mrm.24661. [4] Bennett DA, et al. *Curr Alzheimer Res* 2012;9:646–663. [5] Bennett DA, et al. *J Alzheimers Dis* 2013;33 Suppl 1:S397-403. [6] Bakkour A, et al. *Neurology* 2009;72:1048-1055. [7] Nelson PT, et al. *Acta Neuropathol* 2013;126:161-177.