Accelerated brain parenchymal loss in healthy people above 60.

S. Egorova[1,2], Z. Liptak[1,2], L. Liu[1,2], D. Meier[1,2], N-K. Chen[1,2], R. J. Killiany[3], M. S. Albert[4], C. R. Guttmann[1,2]

[1]Radiology, Brigham and Women's Hospital, Boston, MA, United States, [2]Harvard Medical School, Boston, MA, United States, [3]Departments of Anatomy and Neurobiology, and Neurology, Boston University School of Medicine, Boston, MA, United States, [4]Departments of Psychiatry and Neurology, Massachusetts General Hospital, Boston, MA, United States

Introduction: This study was undertaken to determine the extent of age-related volumetric changes in the brain. It is based on cross-sectional data for healthy people (17-88 years of age) using validated and highly reproducible MRI morphometry/volumetry [1 2]. The aims of the study were to: a) obtain a data-driven age grouping; b) determine brain and tissue compartment relationship with age; c) evaluate the effect of gender on any potential changes.

Methods: A total of 192 subjects from previous studies of normal aging [4] and control subjects from various studies [5] were included. Informed consent was obtained from all subjects. Double-echo axial MRI images of the brain (1.5 T) were acquired [4 5]. Image analysis comprised an automated tissue segmentation into the intracranial cavity (ICC) and subclasses of white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), and WM signal abnormalities (WMSA). Tissue volumes were normalized by the ICC for analysis. Brain parenchymal fraction (BPF) was defined as BPF=(1-CSF)/ICC. An automated nearest neighbor clustering was applied based on Euclidian distance between BPF vs. Age "objects", with a maximum number of clusters set empirically at 2-12. To test differences between age groups, a multivariate analysis of variance (Manova) of multiple variables [BPF, WM, GM, WMSA, Gender] with canonical analysis was performed. A linear regression was estimated from separate lines, same line, separate means, same mean ancova models (age as predictor, volumetric variable as the linear response, and age group or gender as a grouping variable). Fits were compared for differences in slopes and population marginal means using Tukey's honestly significant criterion.

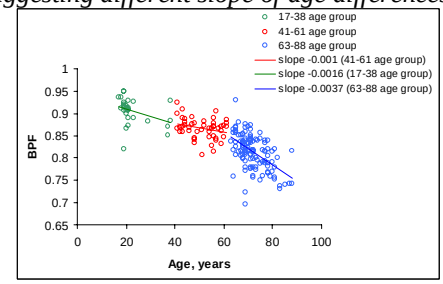
Results: Based on the distribution of the data (Figure) and the pattern of clustering we identified three age groups as 17-38, 41-61 and 63-88 years. Significant differences for medians of volumetric variables between these age groups were found (Wilcoxon rank sum test for unpaired comparisons, $p<0.0001$). The age groups differed significantly according to the Manova. Canonical analysis yielded following linear combinations of the original variables: $c1 = -14.6_{BPF} + 40.6_{WM} + 51.2_{GM} - 45.4_{WMSA} + 0.6_{Gender}$; $c2 = -46.0_{BPF} + 33.6_{WM} + 70.1_{GM} - 27.6_{WMSA} + 0.8_{Gender}$.

Table. Volumetric estimates and slope differences in age groups.

	Age, y.	BPF	GM	WM	WMSA
Mean	22	0.904	0.470	0.429	0.001
Slope		-0.0016	-0.0005	-0.0006[3]	-0.0001
Mean	51	0.866	0.440	0.419	0.001
Slope		-0.001[3]	-0.0005	-0.0009[3]	-0.0003[3]
Mean	72	0.812	0.439	0.366	0.002
Slope		-0.0037[2]	0.0005	-0.0052[12]	0.0001[2]

Significant difference from: 1 - 17-38, 2- 41-61, 3- 63–88 age group .

Figure. Normalized brain parenchymal volume of age groups with linear regression fits suggesting different slope of age differences.



Discussion: The breakdown of the data into age groups as defined by cluster analysis was 17-38, 41-61, 63-88 years of age. Significant differences in brain tissue volumes were found between the three groups. Age differences in BPF and WMSA are well described by three piecewise linear regressions with the slope for the population above age 63 significantly different from the 41-61 age group. WM slopes for the population 63-88 years of age were significantly different from both younger groups. The same line model described age differences of GM. Above age 63 women showed less atrophy than men, yet slopes of BPF vs age were the same. No gender differences in BPF were detected for other age groups. Significant gender differences were detected in GM slopes on age. Possible interpretation on different slopes between age groups: brain development (i.e. synaptic pruning) continued into early adulthood, stable plateau, and degeneration or senescence with degenerative change of brain volume after age 60.

Grant Support: This work was supported by the grant NIH/NIA Grant #P01 AG04953-18. Mrs. M. Polgar-Turcsanyi, Mr. M. Anderson, Mrs. M. Jakab, and Dr. A. Robatino are acknowledged for technical assistance.

References: 1. Wei X et al. *J Magn Reson Imaging* 2002; 2. Warfield S et al. *J Image Guid Surg* 1995; 3. Kikinis R et al. *J Magn Reson Imaging* 1992; 4. Guttmann CR et al. *Neurology* 1998; 5. Killiany RJ et al. *Neurology* 2002.