

# Measuring the effects of aging and gender on regional brain shear stiffness in healthy volunteers with MR Elastography

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**Target audience:** Neuroradiologists, neurologists, and physicists interested in the mechanical properties of the brain.

**Purpose:** Several groups have investigated the use of magnetic resonance elastography (MRE) in neurological diseases including brain tumors<sup>1</sup>, normal pressure hydrocephalus<sup>2</sup> and Alzheimer's disease<sup>3</sup>. Other studies have reported that global brain stiffness decreases with age and one study found that females have less stiff brains than males<sup>4</sup>. Recent publications have presented regional brain property estimates<sup>5,6</sup>. The objective of this study was to evaluate global and regional changes in brain stiffness as a function of age and gender, using improved MRE acquisition and processing that has been shown to provide median stiffness values that are typically reproducible within 1%, in global measurements, and within 2% for regional measurements<sup>7</sup>.

**Methods:** This study was approved by our institutional review board and the subjects were imaged after obtaining written informed consent. A total of 45 healthy (22 males, 23 female) amyloid-negative, cognitively normal subjects in the age range of 56-89 years (mean = 74, median = 76) were included in the study. The subjects were recruited from a longitudinal study of aging in which they had already undergone Pittsburgh compound B positron emission tomography (PiB PET) imaging to determine they did not have an abnormal amyloid burden. Image acquisition included a modified spin-echo echo planar imaging sequence to acquire MRE data with the following imaging parameters: 60-Hz vibration; TR/TE = 3600/62 ms; FOV = 24 cm; 72x72 image matrix reconstructed to 80x80; 48 contiguous 3-mm-thick axial slices; one 18.2-ms motion-encoding gradient on each side of the refocusing RF pulse; x, y, and z motion encoding directions; and 8 phase offsets spaced evenly over one period of 60-Hz motion. MRE postprocessing was performed utilizing a previously described pipeline<sup>7</sup> and can be summarized in 3 steps: 1) calculating the curl of the displacement images; 2) smoothing the data with a quartic smoothing kernel; and 3) calculating the stiffness using an adaptive direct inversion of the Helmholtz wave equation. The median stiffness in the cerebrum, frontal lobes, occipital lobes, parietal lobes, temporal lobes, deep gray matter/white matter (insula, deep gray nuclei and white matter tracts), and the cerebellum were calculated for each volunteer. Median stiffness was then fitted to a multiple linear regression model, using statistical analysis software (JMP® Pro 9.0.1, SAS Institute Inc., USA) with gender and age as the independent model parameters. The software used a Student's t-test to evaluate the probability of the null hypothesis (slope=0) for each independent parameter. The statistical significance of age and gender were evaluated for each region of the brain.

**Results:** A significant negative correlation between age and brain stiffness was observed in the cerebrum ( $p < 0.0001$ ) (Figure 1A), frontal lobes ( $p < 0.0001$ ), occipital lobes ( $p = 0.0005$ ), parietal lobes ( $p = 0.0002$ ), and the temporal lobes ( $p < 0.0001$ ) of the brain. No significant correlation between brain stiffness and age was observed in the cerebellum ( $p = 0.74$ ) (Figure 1B), and the sensory motor regions ( $p=0.32$ ) of the brain, and a weak trend was observed in the deep gray matter/white matter ( $p=0.075$ ). The multiple linear regression model predicted an annual decline of  $0.011 \pm 0.002$  kPa in cerebrum stiffness with a theoretical zero age (y-intercept) of  $3.4 \pm 0.1$  kPa. A gender effect was also observed in the temporal ( $p = 0.0326$ ) (Figure 1C) and occipital ( $p=0.001$ ) (Figure 1D) lobes of the brain, but no significant difference was observed in any of the other brain regions ( $p > 0.2$  for all other regions). The model predicted female occipital and temporal lobes to be 0.228 kPa and 0.0853 kPa stiffer than males of the same age, respectively. Typical T1-weighted images and elastograms are shown in Figure 1E-H.

**Discussion:** This work has demonstrated that regional brain stiffness is heterogeneous and variably dependent on age and gender. Specifically, stiffness of the cerebrum is found to decrease with age by approximately  $-0.011 \pm 0.002$  kPa/year. This value is approximately equal to the 0.0075 kPa/year decline in global brain stiffness previously reported by Sack et al.<sup>4</sup> at a vibrational frequency of 62.5 Hz based on three transverse slices within the cerebrum at the level of the ventricles. However, we found stiffness measurements to be independent of age for deep gray/white matter, cerebellum, and sensory motor regions of the brain. The cerebellum stiffness ( $2.23 \pm 0.18$  kPa) was found to be significantly lower ( $p < 0.001$ ) than the cerebrum stiffness across all subjects, which agreed with findings reported by Sinkus et al.<sup>8</sup> in younger subjects (22-43 years old). In addition, Sack et al.<sup>4</sup> reported that the stiffer cerebrum of women were estimated to be approximately 10 years younger than those of men in an earlier study, but found no correlation with gender in their most recent work<sup>9</sup>. We found only the occipital and temporal lobes' stiffness to be dependent on gender. This finding suggests that region selection could explain the discrepancies in gender effect apparent in the literature. In addition, our processing tries to remove the influence of cerebrospinal fluid and edge effects from our stiffness measurements, which may help isolate tissue-specific characteristics. Dividing the predicted increase in female brain stiffness by the slope of the age curve, it can be estimated that the occipital and temporal lobes of females are approximately 20 and 8 years younger than those of men, respectively. Our study confirms that as the brain ages there is softening, however the changes are dependent on region. In addition, stiffness effects due to gender can exist when making measurements in the occipital and temporal lobes.

**References:** [1] Xu et al. Acta Rad 2007. 48: 327. [2] Streitberger et al. NMR in Biomed 2010. [3] Murphy et al. JMIR 2011. 34(3): 494 [4] Sack et al., NeuroImage. 2009 (46): 652-657. [5] Guo et al., PLoS One 2013. 8: e71807 [6] Johnson et al., NeuroImage 2013 (79):145-152. [7] Murphy et al., Proc. Intl. Soc. Mag. Reson. Med. 2013 (21): 2422. [8] Sinkus et al. J Biomech 2011. 44:1909:1913. [9] Sack et al., PLoS One 2011. 9: e23451.

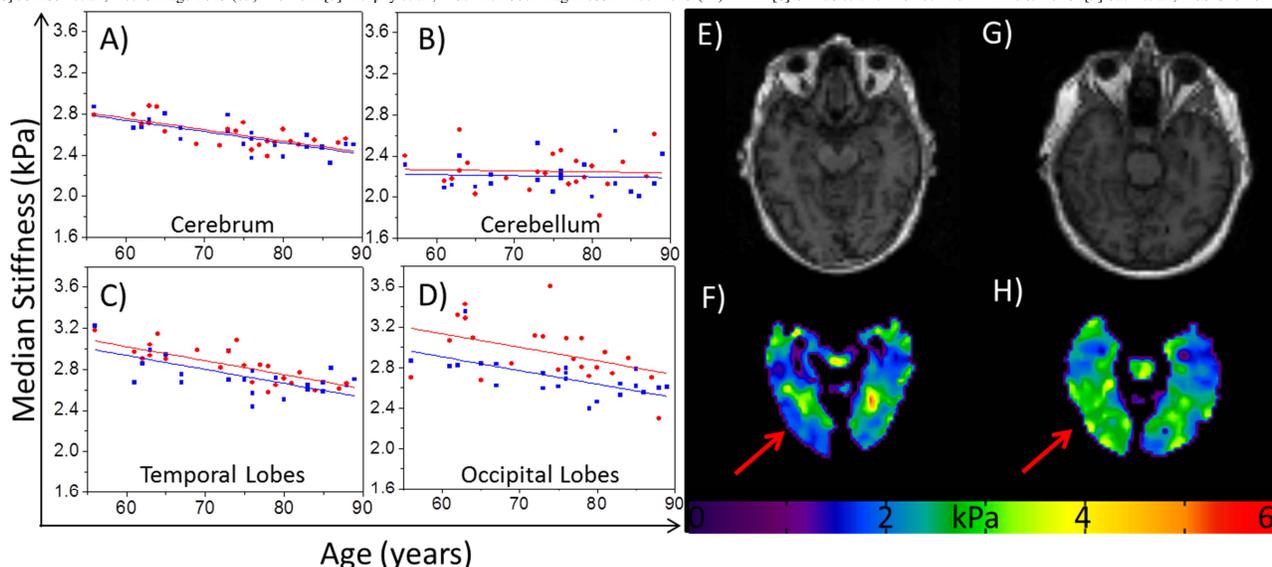


Figure 1: Plot of median brain stiffness (kPa) versus age in male (blue squares) and female (red circles) populations in the A) cerebrum, B) cerebellum, C) temporal lobes, and D) occipital lobes. Trend lines given by the multiple linear regression model are plotted for males (blue solid line) and females (red solid line). For comparison purposes, T1-weighted images (E and G) and the corresponding elastograms (F and H) for a 73-year-old male and a 73-year-old female are shown, respectively. The red arrow points to the occipital lobe of each volunteer.