Regional brain stiffness changes across the Alzheimer's disease spectrum

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Introduction: Alzheimer's disease (AD) is characterized by the progressive impairment of cognitive function, typically beginning with memory. Biomarkers are important tools that improve our understanding of disease etiology, aid in early diagnosis and provide metrics for the testing of candidate therapies. Earlier work demonstrated that global brain stiffness as measured by MR elastography (MRE) is a novel biomarker of AD [1]. The purpose of this work was to measure changes in brain stiffness related to AD on a regional basis and across the full AD spectrum (i.e. cognitively normal → mild cognitive impairment → AD dementia).

Methods: This study was approved by our IRB. We scanned 48 subjects in 4 age- and gender-matched groups after obtaining informed written consent: 16 amyloid-negative cognitively normal control subjects (CN-), 16 amyloid-positive cognitively normal control subjects (CN+), 8 amyloid-positive subjects with mild cognitive impairment (MCI) due to AD, and 8 amyloid-positive subjects with AD. MRE data were collected with a modified spin-echo EPI pulse sequence with the following 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 the 60 Hz motion. The resulting images had 3 mm isotropic sampling and were acquired in just less than 7 minutes. In each subject we measured brain stiffness in 9 regions of interest (ROIs): global, frontal lobes, occipital lobes, parietal lobes, temporal lobes, deep gray matter/white matter (insula, deep gray nuclei and white matter tracts), cerebellum, sensory/motor strip and a summary ROI that included the frontal, parietal and temporal lobes but excluded the sensory/motor strip (labeled FPT in Figure 1). The ROIs for each subject were determined by warping an atlas in standard space to the subject's high resolution T1-weighted image, which was then registered and resliced to the T2-weighted MRE magnitude image. The Kruskal-Wallis test was used to determine if any group-wise differences existed between the 4 groups, and pairwise comparisons were made with the Wilcoxon rank sum test. To estimate the time course of brain stiffness with respect to AD severity, a scatter plot was generated of FPT stiffness versus disease rank (subjects ranked first by clinical classification and then by amyloid load) and the relationship was modeled with restricted cubic splines with 4 knots. Hippocampal volumes were calculated with FreeSurfer (v.5.1) and normalized to total intracranial volume (TIV).

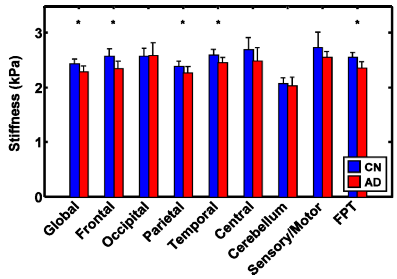

Figure 1. Regional brain stffiness in CN versus AD subjects (*p<0.05).

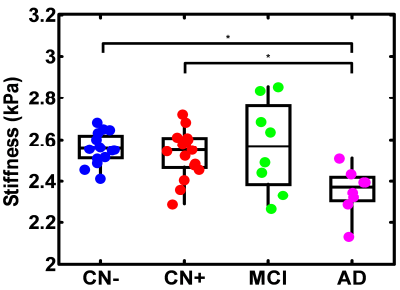

Figure 2. FPT stiffness by group.

Results: Stiffness by region for all CN subjects versus the AD group is summarized in Figure 1 (mean ± standard deviation). These results indicate that changes in brain stiffness follow the known topography of AD as stiffness is significantly decreased in the frontal, parietal and temporal lobes, which contain association cortices that are most significantly affected AD. On the other hand, regions of the brain that contain primary cortices, which include the occipital lobes and sensory/motor strip, demonstrate no significant differences. Based on these results, we generated an optimized FPT region, in which brain stiffness discriminated these CN and AD subjects with 90% accuracy. FPT stiffness in each of the 4 groups is summarized in the box plot of Figure 2. The Kruskal-Wallis test indicated significant differences between groups, and subsequent rank sum tests indicated that both CN groups were significantly different from the AD group. Notably, stiffness within the MCI group is highly variable, but also significantly and inversely correlated with amyloid load (R^2=0.73, p=0.011, Spearman rank correlation).

To estimate the time course of FPT stiffness with respect to AD severity, all subjects were put on a common scale of severity by ranking them first by clinical classification and then by amyloid load (as assessed by PIB PET imaging). As shown in the top panel of Figure 3, when hippocampal volumes (a very well established biomarker of AD) are plotted against disease rank, a highly significant fit is observed that is nonlinear but monotonic (R^2=0.59, p=3.9e-9). Similarly, a highly significant and nonlinear fit is observed when plotting FPT stiffness versus disease rank (bottom panel of Figure 3), but this relationship is non-monotonic (R^2=0.41, p=3.6e-5).

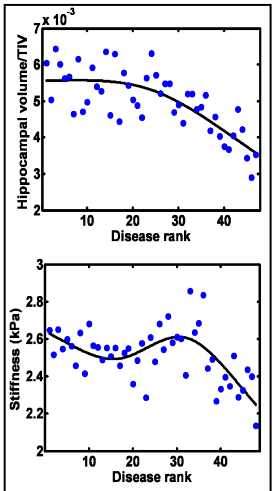

Figure 3. Hippocampal volumes (top) and FPT stiffness (bottom) versus disease rank.

Discussion: The work presented here first reproduces an earlier finding that global brain stiffness is decreased in subjects with AD compared to matched controls [1]. Furthermore, the regional brain stiffness results show that changes in brain stiffness follow the known topography of disease. These results also demonstrate that brain stiffness may follow a unique time course with respect to AD severity compared to existing biomarkers. Whereas neurodegeneration (measured by structural MRI) and amyloid load (measured by PET imaging or CSF assay) progress monontonically with respect to AD severity, similar increases in the MCI phase of the AD spectrum have been reported in functional MRI experiments. For example, Putcha et al. reported that hippocampal activation during a memory task increases in subjects with MCI [2], and Bai et al. also demonstrated increases in default mode network connectivity in MCI [3]. For this reason, we hypothesize that MRE is measuring changes in brain stiffness that are downstream of changes in brain function. Structural alterations that could accompany functional plasticity and also affect brain stiffness include white matter and/or cerebrovascular plasticity.

References: [1] Murphy et al. JMRI 2011. 34(3): 494. [2] Putcha et al. J Neurosci 2011. 31(48): 17680. [3] Bai et al. PloS One 2011. 6(9): e24271.