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Regional brain stiffness changes across the Alzheimer's disease spectrum☆

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ABSTRACT

Magnetic resonance elastography (MRE) is an MRI-based technique to noninvasively measure tissue stiffness. Currently well established for clinical use in the liver, MRE is increasingly being investigated to measure brain stiffness as a novel biomarker of a variety of neurological diseases. The purpose of this work was to apply a recently developed MRE pipeline to measure regional brain stiffness changes in human subjects across the Alzheimer's disease (AD) spectrum, and to gain insights into the biological processes underlying those stiffness changes by correlating stiffness with existing biomarkers of AD. The results indicate that stiffness changes occur mostly in the frontal, parietal and temporal lobes, in accordance with the known topography of AD pathology. Furthermore, stiffness in those areas correlates with existing imaging biomarkers of AD including hippocampal volumes and amyloid PET. Additional analysis revealed preliminary but significant evidence that the relationship between brain stiffness and AD severity is nonlinear and non-monotonic. Given that similar relationships have been observed in functional MRI experiments, we used task-free fMRI data to test the hypothesis that brain stiffness was sensitive to structural changes associated with altered functional connectivity. The analysis revealed that brain stiffness is significantly and positively correlated with default mode network connectivity. Therefore, brain stiffness as measured by MRE has potential to provide new and essential insights into the temporal dynamics of AD, as well as the relationship between functional and structural plasticity as it relates to AD pathophysiology.

1. Introduction

Alzheimer's disease (AD) is characterized clinically by the progressive impairment of cognitive function typically beginning with episodic memory, and pathologically by extracellular amyloid plaques and intracellular neurofibrillary tangles (McKhann et al., 1984). The single biggest risk factor is old age and therefore the number of affected individuals in the industrialized world continues to grow as demographics shift toward an older population (Hebert et al., 2003). AD biomarkers are important tools to improve understanding of disease etiology, aid in early diagnosis and provide metrics for the testing of candidate therapies. In fact, biomarkers have already been incorporated into the most recent criteria for the diagnosis of AD (McKhann et al., 2011), as well as mild cognitive impairment (MCI) due to AD (Albert et al., 2011), and pre-clinical AD (Sperling et al., 2011). Most research on AD biomarkers has concentrated on 5 major modalities. These biomarkers measure 2 different processes associated with the AD cascade: 1. Fibrillar amyloid beta deposition (measured by amyloid positron emission tomography [PET] imaging or cerebrospinal fluid [CSF] assay); and 2. Tau-mediated neurodegeneration (measured by CSF assay, fluorodeoxyglucose 18F [FDG] PET, and structural MRI).

Based on these modalities, Jack et al. proposed a model of dynamic biomarkers across the AD spectrum, which hypothesized that the biomarkers progress monotonically from normal to abnormal in a characteristic temporal sequence (Jack et al., 2010, 2013). This model provides a theoretical framework for how to use multimodal biomarker data to measure an individual's position along the spectrum of AD severity, and work is ongoing to validate the model. However, these 5 biomarkers certainly do not measure all biological processes associated with Alzheimer's disease, and novel biomarkers that measure additional processes would improve the model. Notably, the model does not currently include direct measures of functional and structural connectivity.

Previously, we reported that global brain stiffness as measured by magnetic resonance elastography (MRE) was decreased in subjects with AD compared to age-matched control subjects both with and without a significant brain amyloid load (Murphy et al., 2011). MRE is an

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MRI-based technique to noninvasively measure tissue stiffness (Muthupillai et al., 1995). It is a three step process beginning with the introduction of shear waves into the tissue of interest via an external vibration source. The resulting shear waves are imaged with a phase-contrast MRI pulse sequence by applying motion-encoding gradients that are synchronized to the external vibrations. Finally, the shear wave images are mathematically inverted to calculate a stiffness map, which is also called an elastogram. MRE is already used clinically to measure liver disease severity from the early stages of fibrosis through cirrhosis (Yin et al., 2007). More recently, several groups have begun to apply MRE to the brain to measure the effects of age and sex on brain structure (Arani et al., 2015; Sack et al., 2009), or to investigate the potential of brain stiffness as a novel biomarker of a number of neurological diseases including multiple sclerosis (Streitberger et al., 2012; Wuerfel et al., 2010), normal pressure hydrocephalus (Freimann et al., 2012; Streitberger et al., 2011), intracranial tumors (Murphy et al., 2012b; Xu et al., 2007), and amyotrophic lateral sclerosis (Romano et al., 2014).

The purpose of this work was to measure the relationship between brain stiffness and severity of AD pathophysiology along the entire disease spectrum, and to gain further insight into the biological processes underlying changes in brain stiffness due to AD. To date only measures of global brain stiffness in AD have been studied systematically and elastography thus remains a largely unexplored and potentially unique window into the biological expression of the disease. These aims, respectively, were accomplished by applying recently developed MRE techniques to measure regional brain stiffness in subjects spanning the AD spectrum (i.e., cognitively normal → mild cognitive impairment → AD dementia), and then investigating the relationships between brain stiffness and existing biomarkers.

2. Materials and methods

2.1. Subject recruitment

This study was approved by our institutional review board. After obtaining informed written consent, we scanned 48 subjects in 4 age- and gender-matched groups including 16 amyloid-negative cognitively normal controls (CN−, 8 male, 8 female), 16 amyloid-positive cognitively normal controls (CN+, 8 male, 8 female), 8 amyloid-positive subjects with mild cognitive impairment (MCI, 4 male, 4 female), and 8 amyloid-positive subjects with probable Alzheimer's disease (AD, 6 male, 2 female). These subjects were recruited from the Mayo Clinic Study of Aging (MCSA) and the Alzheimer's Disease Patient Registry. Criteria for the diagnosis of cognitively normal control subjects included: 1. no active neurologic or psychiatric disorders; 2. absence of any ongoing medical problems or their treatments that may interfere with cognitive function; 3. a normal neurological exam; 4. no psychoactive medications; and 5. were independently functioning community dwellers. The diagnosis of probable Alzheimer's disease was made according to the Diagnostic and Statistical Manual for Mental Disorders, III Edition—Revised (DSM-III-R) Criteria for dementia, and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association Criteria (NINCDS/ADRDA) for AD. To ensure the MCI and AD groups had AD pathology, the subjects also were required to have tested positive for brain amyloid load (i.e., PIB SUVR > 1.5).

2.2. PET scans

Quantitative image analysis for PIB PET was done using an in-house, fully automated image processing pipeline as previously described (Jack et al., 2008). Statistics on image voxel values were extracted from automatically labeled cortical ROIs using an in-house modified version of the AAL atlas (Tzourio-Mazoyer et al., 2002). A cortical amyloid PET standardized uptake value ratio (SUVR) was formed by combining the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus ROI values normalized by the cerebellar gray matter ROI of the atlas. The cut-off of 1.5 PIB SUVR for amyloid positivity was previously determined as the optimal threshold for separating high versus low amyloid PET values measured in sample including CN, MCI and AD subjects (Jack et al., 2008).

2.3. MRE acquisition

MRE images were collected with a modified single-shot spin-echo EPI pulse sequence on a 3 T MR imager (SIGNA Excite, GE Healthcare, Waukesha, WI). Shear waves of 60 Hz were introduced into the brain as previously described (Murphy et al., 2011). This system is comprised of an active pneumatic driver (located outside the scanner room), which vibrates a soft, pillow-like passive driver placed under the subject's head. The resulting displacement field was imaged with the following parameters: TR/TE = 3600/62 ms; FOV = 24 cm; BW = ±250 kHz; 72 × 72 imaging matrix reconstructed to 80 × 80; frequency encoding in the right-left direction; 3× parallel imaging acceleration; 48 contiguous 3 mm thick axial slices; one 4 G/cm, 18.2 ms, zeroth- and first-order moment nulled motion-encoding gradient on each side of the refocusing RF pulse synchronized to the motion; motion encoding in the positive and negative x, y and z directions; and 8 phase offsets sampled over one period of the 60 Hz motion. The resulting images have 3 mm isotropic resolution and were acquired in just less than 7 min. Two additional phase offsets with the motion turned off were acquired for subsequent signal-to-noise ratio (SNR) calculations.

2.4. Image processing

The MRE pipeline for measuring regional brain stiffness has been previously detailed, along with an evaluation of its test–retest reliability in young volunteers (Murphy et al., 2013). First, complex phase-difference images in each of the x, y and z motion-encoding directions were calculated by taking the product of the complex-valued image with positive motion encoding and the complex conjugate of the image with negative motion encoding. To reduce slice-to-slice phase discontinuities, constant and slowly varying phase ramps in the acquisition plane were removed by first applying a 2D low pass filter (3 × 3 rectangular window function in k-space) to the complex phase difference images (Murphy et al., 2012a). Wave images were then calculated as the phase-difference between the original complex phase difference images and the low pass-filtered phase difference images.

To create the regions of interest (ROIs) and a brain mask we used a separately acquired T1-weighted IR-SPGR image that was collected with the following parameters: sagittal orientation; frequency encoding in the superior–inferior direction; TR/TE = 6.3/2.8 ms; flip angle = 11°; TI = 400 ms; FOV = 27 cm; 256 × 256 acquisition matrix; BW = ±31.25 kHz; 1.75× parallel imaging acceleration in the anterior–posterior direction; and 200 1.2-mm slice locations. A lobar atlas in a standard template space was warped to the subject's T1 image using a unified segmentation algorithm implemented in SPM5 (Ashburner and Friston, 2005). This algorithm also segmented the T1-weighted image to calculate maps of gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) content in each voxel. The T1-weighted image along with the lobar atlas and the segmentation images were then registered (6 degree of freedom rigid body transformation) and resliced to the T2-weighted magnitude image from the MRE data in order to calculate the regional assignment and the GM, WM and CSF content in each voxel in MRE space. A brain mask was generated by including any voxel in which GM plus WM content was greater than CSF content. The T1-weighted image was also used to calculate hippocampal volumes using FreeSurfer for later use as an established measure of disease severity (Fischl et al., 2002). One scan failed this process, and so