CROSS-CORRELATION OF BIOMECHANICAL, CONNECTOMIC, AND PATHOLOGIC MARKERS IN NEURODEGENERATION AT 7T MRI

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INTRODUCTION

Alzheimer's disease (AD), a progressive neurodegenerative disease thought to be caused by abnormal deposits of amyloid plaques in the cortical gray matter in the brain, is the leading cause of dementia, having an immense impact on the aging population worldwide[1]. Over the progression of AD, damage spreads throughout the brain, shrinking the volume of the overall brain tissue[2]. Early diagnosis of AD is still challenging due to subtle microstructural changes, which is particularly troubling, as most treatments for AD can only be used to slow its progression, not reverse it, and are often far more successful when started early. β-amyloid can be detected through the utility of positron emission tomography (PET) with aid of a radioactive, but this procedure is invasive, leading to a profound need to identify non-invasive correlates of AD pathologies.

MR Elastography (MRE) is a technique for determining the mechanical response of tissues using applied harmonic deformation and motion-sensitive MRI. Performing MRE on human brain can provide information on different structures within brain tissue based on their mechanical properties, and pivotal studies applying MRE have shown a progressive softening of white and gray matter tissue in AD patients in regions in line with the known topography of AD pathology[3,4]. Another potential non-invasive diagnostic tool is diffusion tensor magnetic resonance imaging (DTI), which provides a metric for understanding the integrity of microstructure[5]. In addition to changes in signal intensity in the white matter due to aging, previous DTI studies have also identified changes in DTI signal intensity in gray matter regions[6,7], making it a region of interest to study in aging and neurodegeneration.

Additionally, studies at 3T have found correlations between MR Elastography (MRE) and DTI metrics in small white matter structures in young, healthy individuals[8,9], but low imaging resolution limited the specificity of the results in small regions due to partial volume effects.

Leveraging non-invasive ultra-high field (UHF), 7 Tesla (7T) MRI, with increased signal-to-noise ratio and improved soft tissue contrast afforded by UHF allows us to accurately map tissue microstructure. *In this study we aim to use 7T MRE, 7T DTI, 3T amyloid-PET, and cognitive testing results to determine the relationships between these metrics in a cohort of older individuals with either normal cognition, mild cognitive impairment (MCI), or AD.*

METHODS

Two scanning sessions (7T MRI and 3T PET, Fig 1A) and the Preclinical Alzheimer Cognitive Composite (PACC) test were performed on 14 subjects (Avg. age 70.3±5.2 years) determined to be cognitively normal (CN), and 6 subjects (Avg. age 70.0±9.4 years) determined to have MCI or AD. All MCI/AD patients had a consensus diagnosis of cognitive impairment and a Clinical Dementia Rating >4.0 in the Clinical Dementia Rating Scale Sum of Boxes.

Full brain coverage MRE (using a custom SE-2D-EPI-based sequence[10]) was performed at 1.1mm isotropic resolution and 50Hz vibration frequency[11], using a 32-channel head coil (Nova Medical) on a 7T Siemens Magnetom MRI scanner (TR/slice=140ms, TE=65ms, GRAPPA=3, Partial Fourier 7/8). Raw data were collected and analyzed as described in Triolo, *et al.*[12] to calculate the absolute value of the complex shear modulus ($|G^*|$).

A high-angular-resolved diffusion MRI sequence was acquired with 1.05 mm isotropic resolution (b=1500 s/mm2, reversed-phase encoding in anteroposterior and posteroanterior directions for paired acquisition in 68 directions). The Diffusion pre-processing was performed using the human connectome project (HCP) pipelines, adjusted to account for significant eddy currents.[13]. This allowed us to estimate whole brain maps of mean diffusivity (MD) and fractional anisotropy (FA). Segmentation of brain regions was performed on an MP2RAGE T1scans ($0.7mm^3$) using Freesurfer[14] and regional masks were co-registered to the MRE space and DTI space using SPM[15]. SPM was also used to estimate the percentage area of CSF for each region.

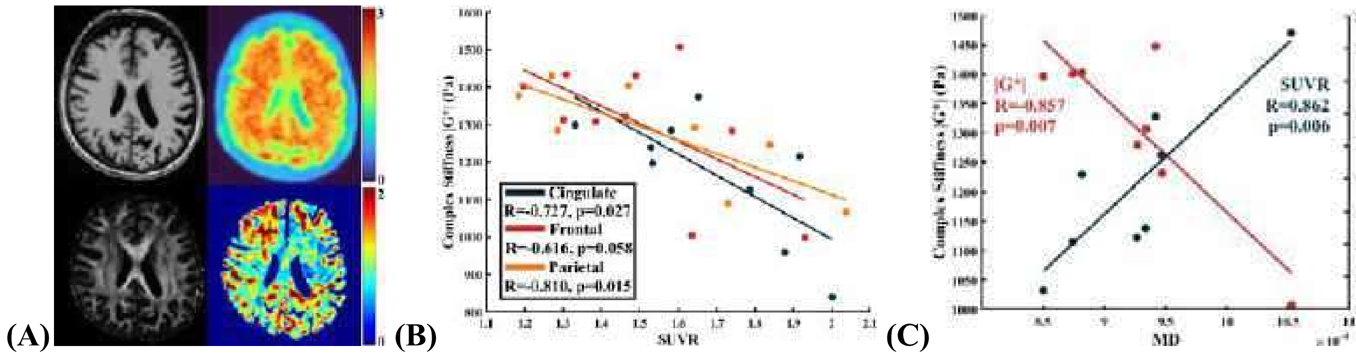

***Figure 1: (A) Top:** T1 (left), PET (right), Bottom: FA (left), and |G*| (right) maps for one subject with MCI, **(B)** Linear correlations between |G*| and SUVR in three cortical brain regions, and **(C)** The linear correlations between |G*| and MD, and SUVR and MD in the temporal cortex.*

Subjects also underwent a Siemens Biograph mMR simultaneous PET-MR scan to measure Aβ burden using F18-labeled florbetaben using FDA standardize protocols. Average selective uptake value ratio (SUVR), FA, MD, and |G*| were calculated per cortical region of interest as specified in Palmqvist, *et al.*[16]. All MCI/AD subjects and one CN subject were determined to be Aβ-positive. We performed multiple Shapley Regressions in subjects with amyloidosis (subjects whose average SUVR are above the region threshold as described in Bullich, *et al.*)[17] in five PET-relevant brain regions (cingulate, frontal, parietal, temporal, and palmqvist-early)[16] with combinations of the different imaging metrics and PACC that were acquired for each subject.

RESULTS

We found significant differences (one-tailed, unequal variance t-test, $p<0.05$) between the CN and AD/MCI groups in |G*| of the hippocampus and frontal lobe, and SUVR of all brain regions investigated. A significant negative correlation was found between average SUVR and |G*| in the cingulate and parietal cortical regions in the Aβ-positive subjects, with a trending correlation in frontal (Fig 1B). We also found a significant positive correlation between SUVR and MD, and a negative correlation between |G*| and MD in the temporal gray matter (Fig 1C). There was a significant negative correlation between SUVR and PACC, and positive correlation between |G*| and PACC, in all regions.

From the Shapley Regressions (Fig 2 A,B), excluding PACC, |G*| was the best predictor of SUVR in subjects with amyloidosis in all brain regions tested, apart from the temporal and parietal lobes, where MD was a better predictor. Once again, excluding PACC, SUVR was the best predictor of |G*| in subjects in all brain regions tested, apart from the temporal lobe, where MD was a better predictor.

DISCUSSION

The negative correlation between |G*| and SUVR in brain regions initially impacted in MCI/AD progression is consistent with a previous investigation, supporting the hypothesis that tissue degeneration caused by Aβ accumulation results in tissue softening. The Shapley regression analyses demonstrated that SUVR and |G*| were the most important imaging covariates in their corresponding multi-regression analyses for multiple brain regions, which is promising for finding correlates of PET through MRE.

MD being the best predictor of SUVR and G* in the temporal and parietal cortexes is consistent with previous investigations of neurodegenerative and age-related brain changes in gray matter. Specifically, correlations between SUVR or |G*| and MD, but not SUVR and |G*| in the temporal cortex may be indicative of cascades which contribute to Aβ deposition, microstructural damage, and tissue softening and degradation. Additionally, similar correlation coefficients between PACC and |G*|, and PACC and SUVR in all brain regions has interesting implications about use of MRE and DTI instead of PET for diagnosing amyloidosis with cognitive impairment.

One limitation of this study is that a more robust MRE inversion algorithm would benefit the high-resolution allowed by 7T, resulting in even more detail. This study is limited by a small sample size, limiting statistical power, so future studies should look to include larger cohort of subjects diagnosed with MCI/AD. Despite these challenges, our multi-modal biomechanical imaging and analysis framework has promise to determine relationships between a multitude of MRI and PET measures for AD and MCI subjects, providing a physical understanding between tissue mechanics and AD pathophysiology.

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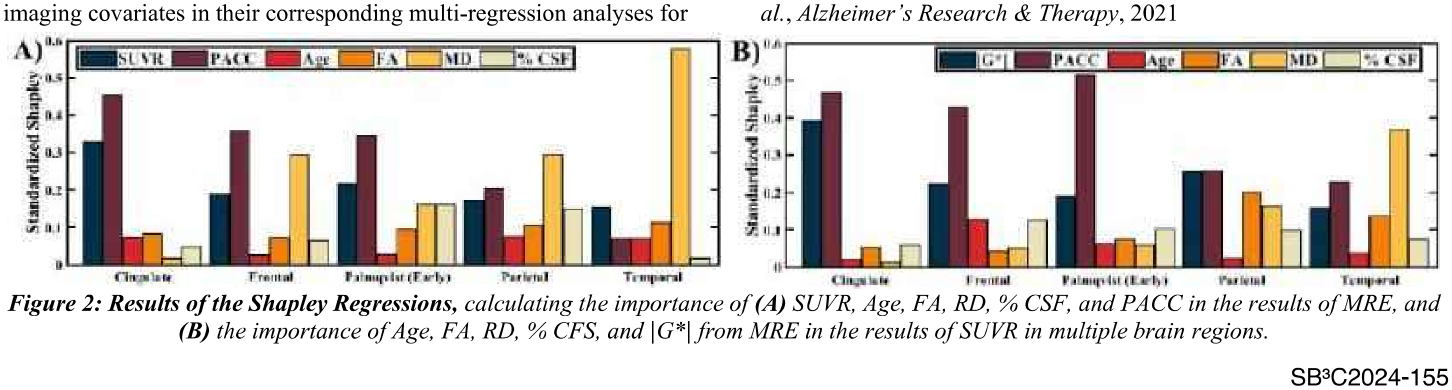

***Figure 2: Results of the Shapley Regressions,** calculating the importance of **(A)** SUVR, Age, FA, RD, % CSF, and PACC in the results of MRE, and **(B)** the importance of Age, FA, RD, % CFS, and |G*| from MRE in the results of SUVR in multiple brain regions.*