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REGIONAL CORRELATION OF STIFFNESS AND PERFUSION IN THE HUMAN BRAIN AT 7T MRI THROUGH MR ELASTOGRAPHY AND ARTERIAL SPIN LABELING TECHNIQUES

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INTRODUCTION

The mechanical properties of the brain give us insight into disease states and open avenues for new methods of medical diagnosis[1]. It is known that brain tissue gets softer as we age[2], but it is unknown whether and how tissue property changes are related to the branched cerebral vascular system in health and disease. Research suggests that changes in cerebral blood flow may be correlated with cognitive deficits in mild cognitive impairment[3], amyloid-beta deposits in Alzheimer's disease (AD)[4], and even diseased liver tissue[5]. However, there is limited research investigating the relationship between perfusion and tissue stiffness in the healthy human brain. In Alzheimer's disease it is unknown how the cascade of associated events contributes to its pathogenesis, but amyloid-deposits, tau tangles, tissue softening, hypoperfusion, and metabolic changes are disease correlates. It has been shown in one preliminary study that perfusion, stiffness, and flux rate are connected in the brain due to higher intravascular pressure that is present in small vessels, coupled with the constriction of vessels in non-compliant tissue[6]. This suggests that perfusion, an indicator of cell metabolic activity and blood volume, will have an impact on the measurable mechanical properties of brain tissue and can be used as a biomarker of underlying pathology. In this study, we utilized the advanced neuroimaging tools of Magnetic Resonance Elastography (MRE) and Arterial Spin Labeling (ASL) to quantify brain stiffness and perfusion non-invasively by voxel. First, a modular pipeline for the post processing and correlation of stiffness and perfusion was developed and used to analyze the collected data from a young control cohort with no known disease. This preliminary dataset serves as a proof-of-concept investigation into how these two metrics may be related in health and disease states of the human brain. Accordingly, the objective of this study was to collect, process, and compare stiffness and perfusion MRI data in a healthy cohort to determine whether these two factors may be correlated.

METHODS

In this study, we obtained pulsed ASL and MRE data from eight healthy volunteers aged 20-35 on a Siemens Magnetom 7T MRI scanner with a 32-channel head coil. The MRE sequence was an echo-planar spin-echo 2D pulse sequence with 3D motion-encoding gradients (TE=70ms, TR=5600ms, GRAPPA=3, 1.1mm isotropic resolution)[7] and a custom pneumatic actuator applied vibrations at 50Hz[8]. The MRE phase magnitude images were masked using SPM12[9], denoised using a MP-PCA algorithm[10] and unwrapped using Segue Phase Unwrapping[11]. The resulting unwrapped displacement data was used to calculate the magnitude of the complex shear modulus (|G*|) using an iterative nonlinear viscoelastic inversion of the time-harmonic Navier's equation[12]. Also acquired at 7T, a PASL sequence was used with EPI readout (TE=39ms, TR=5000ms, 25 repeats, 3.5mm isotropic resolution). Arterial spins were labeled by a 10cm inversion slab proximal to the image slices, with the labeling method Q2TIPS[13]. Subtraction, Bayesian Inference, inversion of the kinetic model of label inflow, and equilibrium magnetization calculations from a proton density weighted (M0) image were used to acquire quantified cerebral blood flow (CBF) in ml/100g/min in accordance with the recommended ASL whitepaper implementation summarized by equation (1) below[14].

$$CBF = \frac{6000 * \lambda * (SI_{control} - SI_{label}) * e^{\frac{TI}{T_{1,blood}}}}{2 * \alpha * TI_1 * SI_{PD}} \quad (1)$$

FreeSurfer[15] segmentation was used with a custom MATLAB script to calculate the correlation coefficient of stiffness and perfusion in gray and white matter regions across subjects. Only whole brain white matter was analyzed based on its low SNR due to high arterial transit time and relatively low perfusion[16]. During analysis, images were visually checked and regionally evaluated based on mean, standard deviation, and volume to determine inconsistencies; no subjects were removed as outliers.

RESULTS

After all subject data was processed and co-registered to the matrix space of each respective T1 image, 3D perfusion maps and elastograms were obtained for each subject; an example of these can be seen in **Figure 1**. As expected, gray matter regions, when averaged across subjects, had higher perfusion and lower stiffness than white matter regions (44.8 ± 4.86 vs. 34.2 ± 8.73 ml/100g/min and 1.57 ± 0.25 vs. 2.42 ± 0.29 kPa, respectively). These findings are consistent with brain stiffness as measured by the magnitude of the complex shear modulus (|G*|) and perfusion values in existing literature.

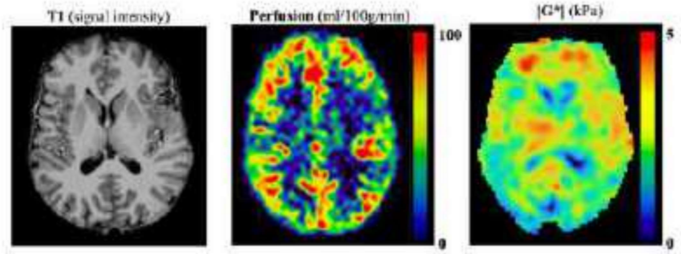

Figure 1: Exemplary axial slice of T1-weighted signal intensity image, perfusion map in ml/100g/min, and elastogram in kPa.

Furthermore, our analysis showed varying strengths of inverse correlation between stiffness and perfusion in some gray matter regions of the brain. Within a cortical gray matter mask, stiffness and perfusion show a strong inverse correlation across subjects (p-value=0.0121, correlation coefficient=-0.823, **Figure 2**). The frontal lobe showed a similar result, with a p-value of 0.0206 and correlation coefficient of -0.787. The white matter across subjects showed a similar, though not statistically significant trend (p-value=0.119, corr. coefficient=-0.596).

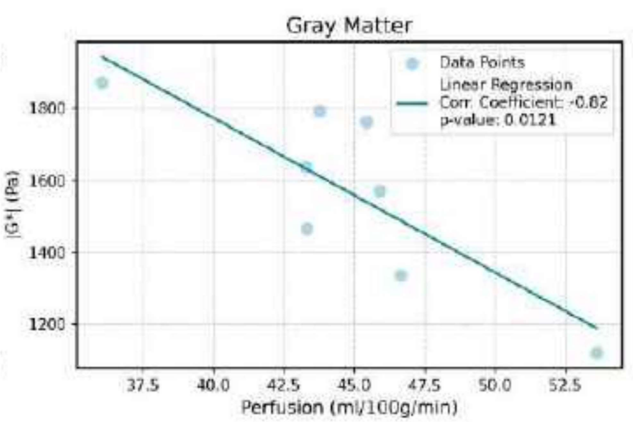

Figure 2: Inverse correlation of stiffness and perfusion in the cortical gray matter, across subjects.

DISCUSSION

Our results showed a strong inverse correlation between stiffness and cerebral blood flow (perfusion) in the healthy human cortex. This result supports our hypothesis that increased blood flow is related to reduced stiffness due to an increase in the relative size of vascular structures[6], a trend that is also consistent with existing research showing reduced whole-brain stiffness following exercise[17], and therefore increased perfusion[18].

These preliminary results, suggesting that there is a measurable correlation between stiffness, a mechanical property of tissue, and perfusion, a measure of blood delivery within tissue, may indicate an underlying biological mechanism that must be investigated further. ASL is unique in the respect that by measuring the delivery of blood to the brain tissue, it is a metric of brain health at the capillary bed level[19]. Unlike other vasculature scans, such as time of flight (TOF) angiography, ASL measures blood delivery rather than blood vessel characteristics. The establishment of correlations between stiffness and perfusion could enhance our understanding of disease pathology in Alzheimer's Disease and other neurodegenerative diseases by highlighting the interplay between tissue mechanics and metabolic and neuroinflammatory changes. To do so, further investigation of this relationship is needed to establish a baseline in the healthy brain. Future work on this study will be accomplished by increasing the pool of healthy controls, acquiring higher resolution and enhanced SNR perfusion data with a pseudo-continuous ASL sequence, and investigating smaller brain regions of interest with different levels of vascularity.

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