Mapping of ApoE-E4 Related White Matter Damage using Diffusion MRI

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INTRODUCTION

Alzheimers Disease (AD) is a multi-faceted progressive neurodegenerative disease that leads to cognitive decline. The exact physiological pathway that leads to cognitive decline is not yet known. However, postmortem histological studies of AD have a distinct signature of beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs). Pittsburgh Compound B (PiB) binds to beta-amyloid plaques and have been used to image disease progression using invasive PET imaging. Both PET and postmortem histology have provided a map of the anatomical progression of plaques and tangles in AD from the limbic regions out towards the cortex in two distinct paths - one anterior and one posterior. The paths eventually merge along the cingulum bundle and continue moving outwards to the cortex. PET studies, however, are only useful after the formation of plaques and tangles. Diffusion Tensor Imaging (DTI) may be able to detect tissue changes in normal and mildly cognitively impaired (MCI) subjects before the onset of plaques and tangles leading to early in-vivo detection of AD and better characterization of the disease process.

A number of factors including genetics and vascular status have been proposed as the major indicators of developing AD. Currently, the strongest indicators for AD are age and ApoE status. This suggests that no single other factor may lead to AD. It has been hypothesized that perhaps a combination of vascular insults combined with a genetic predisposition (presence of ApoE4 allele) may lead to AD. To isolate the areas of the brain preferentially impacted by ApoE4, our study will correlate DTI measures with clinical dementia rating (CDR), age, Framingham Coronary Risk Score (FCRS) and ApoE4 status, allowing us to remove cognitive decline, age and vascular disease from ApoE4 related white matter (WM) damage..

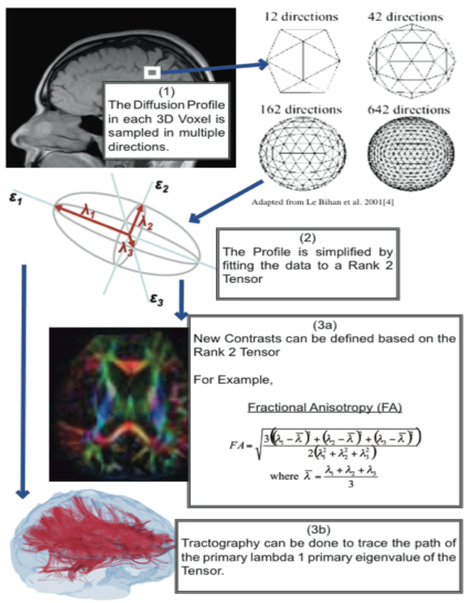

Figure 3: Illustration of Single Fiber DTI Processing

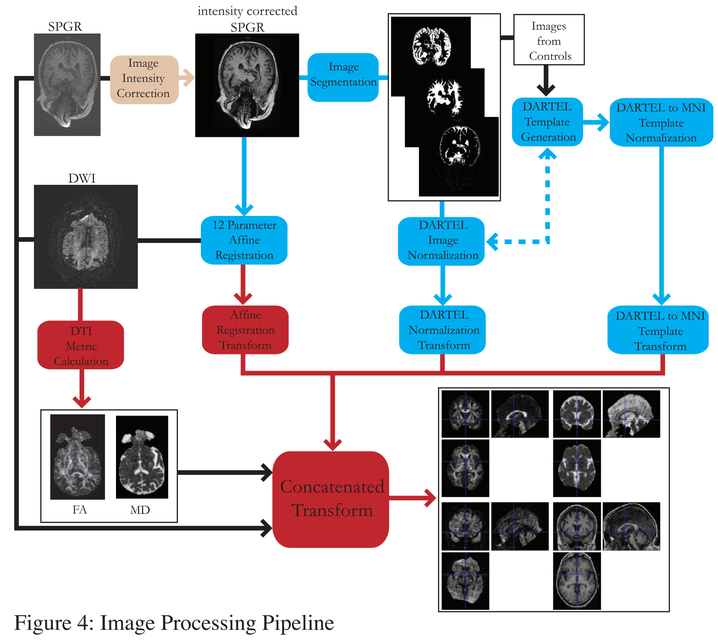

Figure 4: Image Processing Pipeline

BACKGROUND AND SIGNIFICANCE

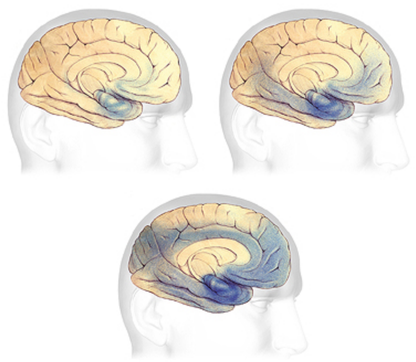

Figure 1:
Pattern of Disease Progression in AD

Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2011; 7:280-292

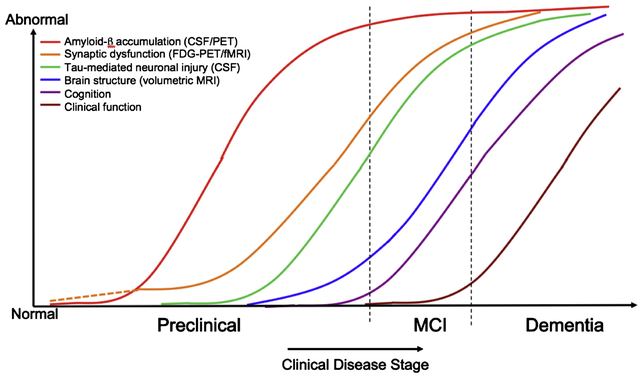

Figure 2:
Methods of Detecting Dementia

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Genetic Factors: ApoE

Apolipoprotein E (ApoE) is a class of proteins found in chylomicron and intermediate- density liporoteins (IDLs). They bind to a specific liver cell receptor. ApoE is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. It was originally discovered to play an important role in lipoprotein metabolism as well as cardiovascular disease. APoE is polymorphic with isoforms: ApoE2, ApoE3 and ApoE4. This translates into 3 allels of the gene: Normal, ApoE-ε3, and the dysfunctional ApoE-ε2 and ApoE-ε4. The ε4 variant of the gene is the largest known genetic risk factor for Alzheimer Disease and is also associated with atherosclerosis and impaired cognitive function. The exact mechanism that causes the ε4 variant to increase risk of AD is not known, but it is postulated that it is related to its interaction with amyloid, specifically the aggregates of beta-amyloids (Aβ) characteristic of AD. 40-65% of AD patients have at least one copy of the ε4 allel. However, ApoE-ε4 is not strictly a determinant of the disease about 1/3 of the patients are APoE-ε4 negative[14]. Moreover some ApoE-ε4 homozygotes never develop AD. ApoE-ε4 heterozygotes, however, has a significantly increased risk for AD.

Diffusion Weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI)

Diffusion Tensor Imaging (DTI) is a Magnetic Resonance Imaging (MRI) technique that allows us to characterize the diffusion profile of tissue by measuring the diffusion coefficient of the tissue in multiple directions. DTI is one of the many DWI techniques, but is unique in that it models the 3D diffusion profile as a rank-2 tensor. The most common application of the technique is to image white matter tissue in the brain. Because white matter tissue in the brain is made up of mostly myelinated bundles of neuronal axons, the diffusion profile highly favors the direction of the neuron bundle. In other words, diffusion along the neuron bundle is much larger than perpendicular to the bundle. To characterize this phenomenon, new contrasts based on the shape of the diffusion profile can be formed. The primary direction allows the path of the neuron bundle to be traced through tractography.

METHODS

Sample

59 subjects with ages ranging from 70 – 86 years were recruited from 3 different sites in a prospective longitudinal study of vascular contributions to aging and cognitive impairment, alone or in combination with AD. ApoE-ε4 positive (29 subjects carrying at least one ε4 allele) and ApoE-ε4 negative (30 subjects). Vascular risk was assessed using the 10-year Framingham Coronary Risk Score (FRCS) and the subjects were categorized either as high or low vascular risk. Dementia staging was performed using the Clinical Dementia Rating (CDR) system.

MR Imaging

MR imaging was performed on three 3T scanners and one 4T scanner. A rigorous image harmonization routine was performed to ensure all sequences produced comparable images from the different scanners. T1-weighted anatomical images (SPGR / MPRAGE) were used to coregister all the images to a common space using SPM's DARTEL Algorithm. b0 maps from the Diffusion images were registered to the T1 images using an affine transformation. Both the affine as well as non-affine transformations were concatenated to achieve coregistration for FA across all the subjects. Statistical Parametric Mapping was performed using SPM8. ApoE-ε4 status, CDR scores, FRCS Category, Age as well as gender were used as covariates and factors in the Design Matrix.

RESULTS

ApoE-ε4 related loss of FA was found most prominently in the parahippocampal regions (Fig.6 - Left) and did not overlap with regions that correlated with Age and CDR (Fig.6 - Middle). CDR scores correlated most with the posterior fornix tracts (Fig.6 -Right) in blue whereas the significant voxels for both ApoE-ε4 (red) as well as Age (green) resided more in the anterior regions surrounding the fornix and corpus collosum. A hemispheric asymmetry was observed with more Age-related significant voxels on the left hemisphere, consistent with previous studies.

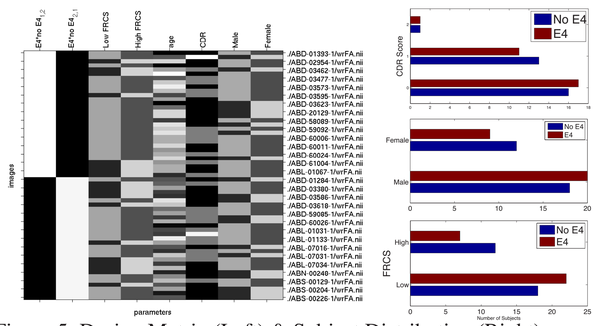

Figure 5: Design Matrix (Left) & Subject Distribution (Right)

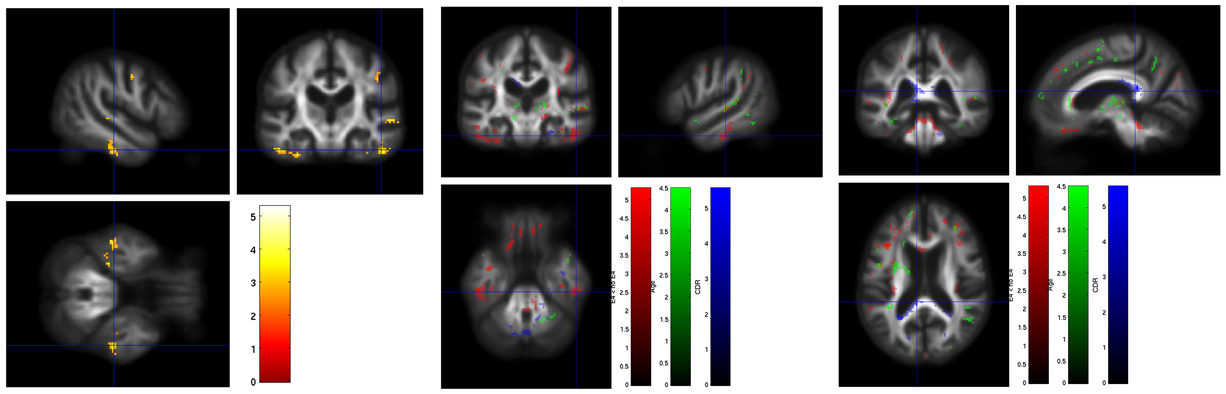

Figure 6: Results of Voxel-based Analysis (VBA)

ApoE4<No ApoE4 P<0.05 (Uncorrected) 10 Voxel Clustering Threshold (Left)
Overlay of Correlated Voxels of ApoE4, Age and CDR P<0.05 (Uncorrected) (Right)

DISCUSSION

Our study shows promising results for separating the effects of ApoE-ε4, Normal Aging and dementia severity when performing large scale MR imaging studies using Diffusion MR. Both the ApoE ε4 and CDR effects (parahippocampal gyrus and fornix) are integral components of the episodic memory system, which is highly vulnerable to neurofibrillary degeneration in AD. The involvement of the medial temporal-diencephalic system in Vascular Cognitive Impairment is less prominent and more variable. Future work in analyzing the complete N>200 dataset will give us the statistical power to investigate the anatomical effects of vascular factors as well as differentiate the cognitive effects of WM damage by correlating individual ROIs with cognitive scores.

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