Mapping of Vascular Dementia Using Diffusion MRI, Genetic Factors and Clinical Scores

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ABSTRACT

Large-scale clinical studies, such as the Aging Brain study of Vascular Dementia, generate large amounts of imaging and non-imaging clinical data. Traditional approaches of analysis have tended to separate the non-imaging from the imaging clinical data with little integration between the two[1-7]. I intend to use simple ROI- based regression analysis to correlate diffusion MRI metrics, such as Fractional Anisotropy (FA) and Mean Diffusivity (MD), with behavioral parameters relating to memory function. In order to achieve the needed Contrast to Noise Ratio (CNR) to do this analysis, I have to improve the qualify of our tissue diffusivity measurements (1) by removing the undesired partial volume noise signal of the Cerebral Spinal Fluid (CSF)[8], [8], [9] and (2) by using a two tensor model to recover two different measurements of tissue statuses in voxels where there are fiber crossings[10], [11]. This approach is in line with the hypothesis that there are two types of mild cognitive impairment (MCI), one that has an amnestic component and another without.The type with the amnestic component ishypothesized to be pre- Alzheimer Disease (AD)[12]. This novel approach aims to allow researchers elucidate differential damage to white matter pathways in vivo, in hopes that this will eventually allow us to investigate the different degenerative patterns that separate AD and non- AD MCI.

SPECIFIC AIMS

My work focuses on Diffusion Weighted Imaging (DWI) of the human brain, in particular, relating to the imaging of neurodegeneration and aging. Diffusion Weighted Imaging and Diffusion Tensor Imaging (DTI) encompasses numerous types of acquisition and processing techniques that have shown promise in imaging White Matter (WM) in the brain. Using these diffusion-based metrics of white matter integrity, the ultimate aim of my thesis is to relate differential damage back to behavioral and clinical measures, specifically memory test scores. By combining imaging and clinical information, I hope to be able to differentiate mechanisms that lead to different types of neurological decline.

AIM 1: To Develop a Method of Linking Imaging Data to Behavioral Measures of Memory Function
Hypothesis: DTI metrics in tract-based ROIs such as the fornix and cingulum correlates more strongly to memory decline than general genetic biomarkers such as ApoE-ε4.

AIM 2: To Form Multi-Tensor DTI Tracts based on ICA Tractography
Hypothesis: By resolving two tensors in fiber crossing regions, we will be able to improve our estimates of DTI metrics, such as FA and MD.

AIM 3: To Perform CSF Partial Volume Correction
Hypothesis: By removing the CSF Partial Volume within each voxel we will improve our estimates of DTI metrics, such as FA and MD.

AIM 4: To Perform Data Harmonization
Hypothesis: By adding site and MRI information into our regression model, we will be able to remove any undesired statistical confounds associated with lack of data harmonization.

BACKGROUND AND SIGNIFICANCE

Aging Population, Dementia and Alzheimer Disease

Neurodegenerative diseases, such as Alzheimer Disease and other related Dementias, impact cognitive function leading to a decline in the patient's memory and executive function. Although the development of these diseases usually leads to a decline in the quality of life for the patient, the costs of such neurodegenerative decline are not limited to the patient alone. Due to the patient's decline in cognitive function, there is a substantial emotional and psychological impact on the patient's family. This is compounded by the decrease in the birth rate in most developed nations leading to the Aging Population phenomenon, as shown in an increase in the mean age in the population of the United States. The decrease in birth rate also means that the elderly has fewer children to help care for them during their later years. It has become increasingly important to keep the aging population healthy to defray the societal burden of caring for the aged.

Currently, definitive diagnosis of most neurodegenerative diseases is only possible through autopsy; therefore there is a great need for accurate biomarkers that will allow for prospective diagnosis. Structural MRI has been widely accepted as the method of choice, but due to the similarities in brain tissue loss, it has been ineffective in differentiating different types of neurodegeneration[12]. This is especially true at an individual level. Moreover, structural MRI analysis does not readily show white matter damage, which could explain complex behavioral changes that occur during AD. Damage in these white matter connections can cause complex decline in cognitive function not expected when functional imaging localized damage to only the processing regions in the cerebral cortex[7]. Our ability to differentiate decline in different regions of the brain will enable us to elucidate a better understanding of what underlying mechanisms cause the different pathways of neurodegeneration. This is not only helpful in the staging of diseases but also provides a starting point for developing treatment and/or preventative measures for neurodegenerative disorders.

Genetic Factors: ApoE

Apolipoprotein E (ApoE) is a class of proteins found in chylomicron and intermediate- density liproteins (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.

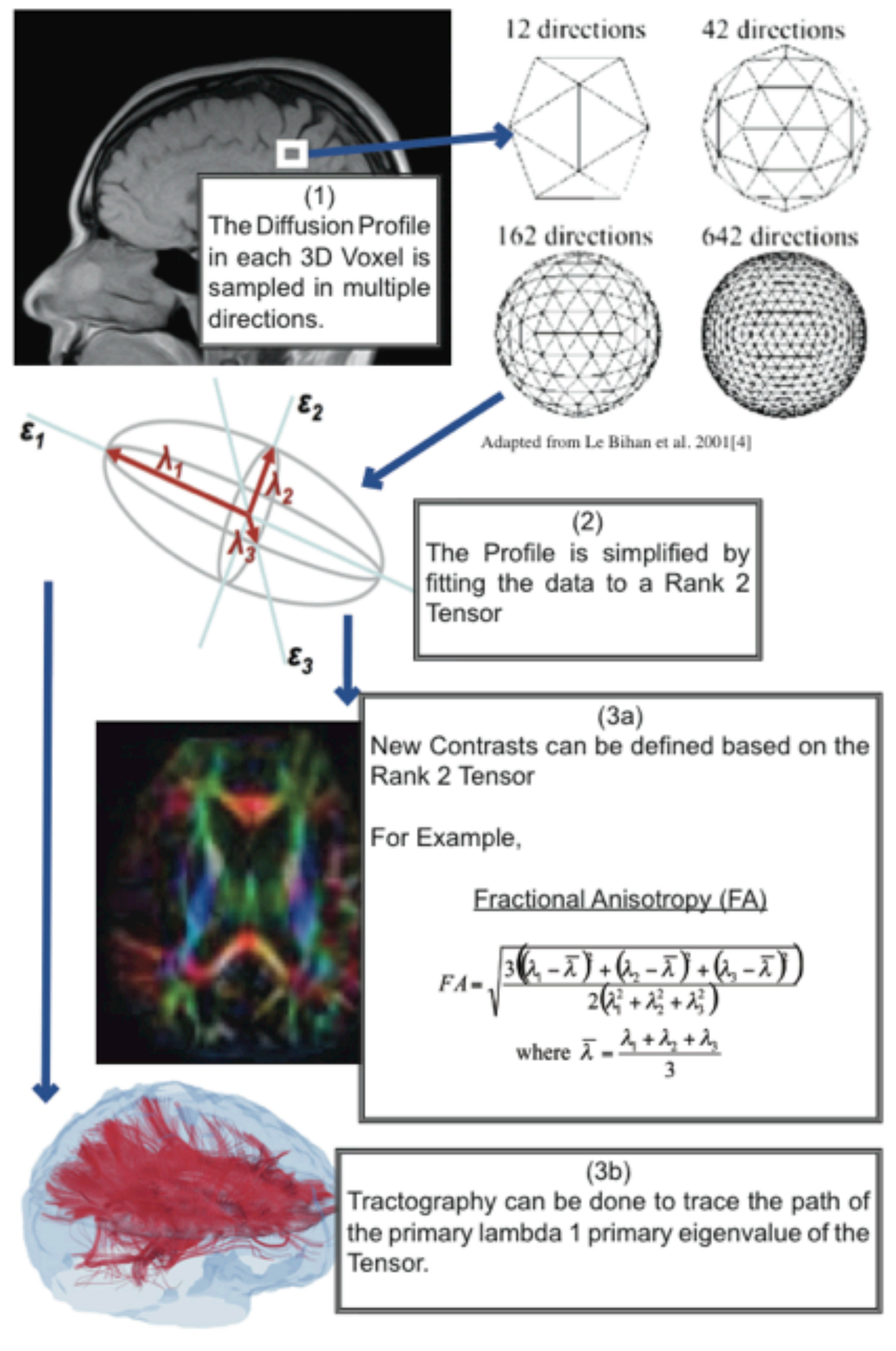


Figure 1: Illustration of Single Fiber DTI Processing

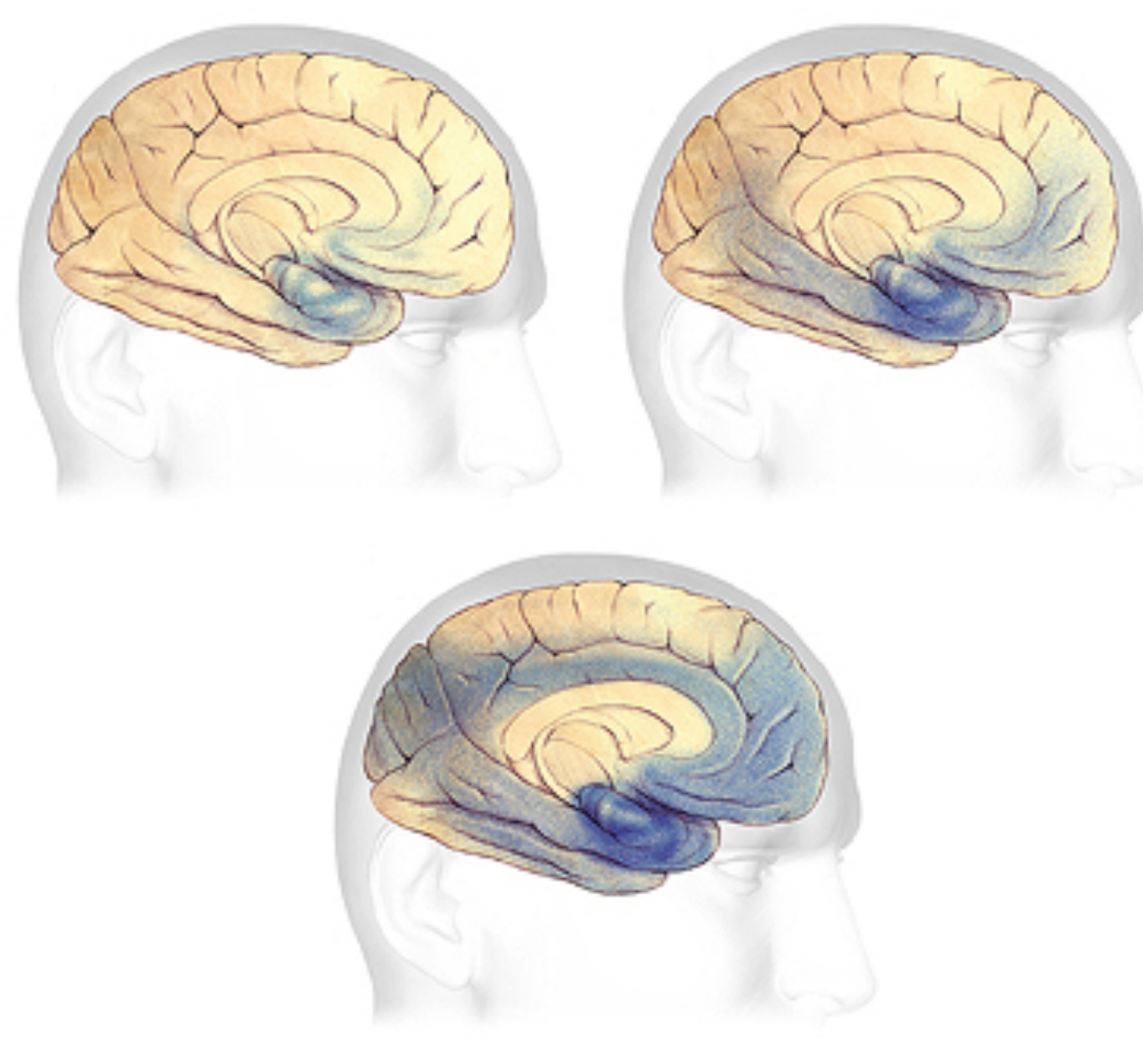


Figure 2:
Pattern of Disease Progression in AD

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

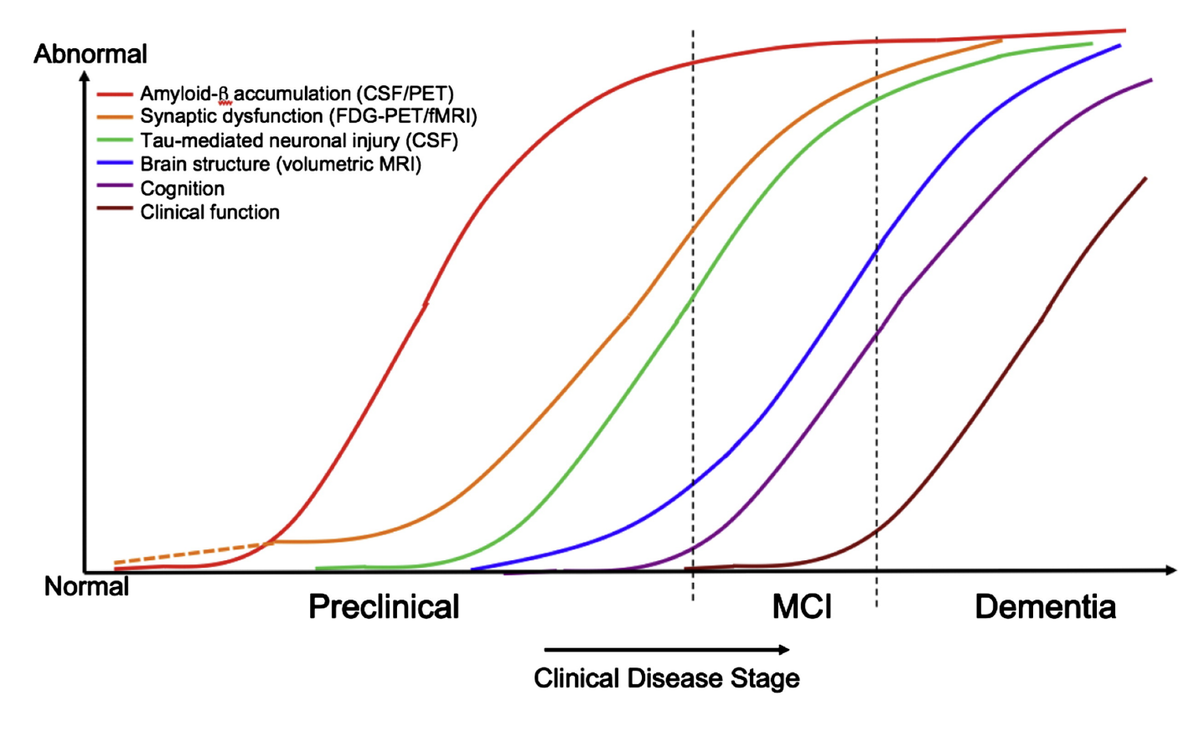
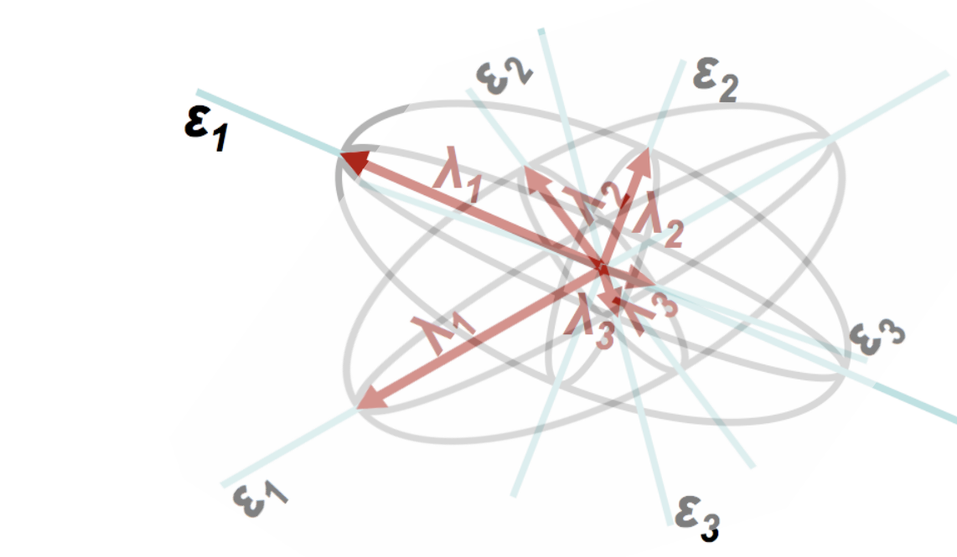


Figure 3:
Methods of Detecting Dementia

Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2011; 7:280-293

METHODS



Single Tensor DTI

$$\frac{S^i}{S_0} = e^{-b\gamma^T D\gamma} + error$$

Dual Tensor DTI

$$\frac{S^i}{S_0} = f e^{-b\gamma^T D_1\gamma} + (1-f) e^{-b\gamma^T D_2\gamma} + error$$

Figure 4: Dual Tensor DTI

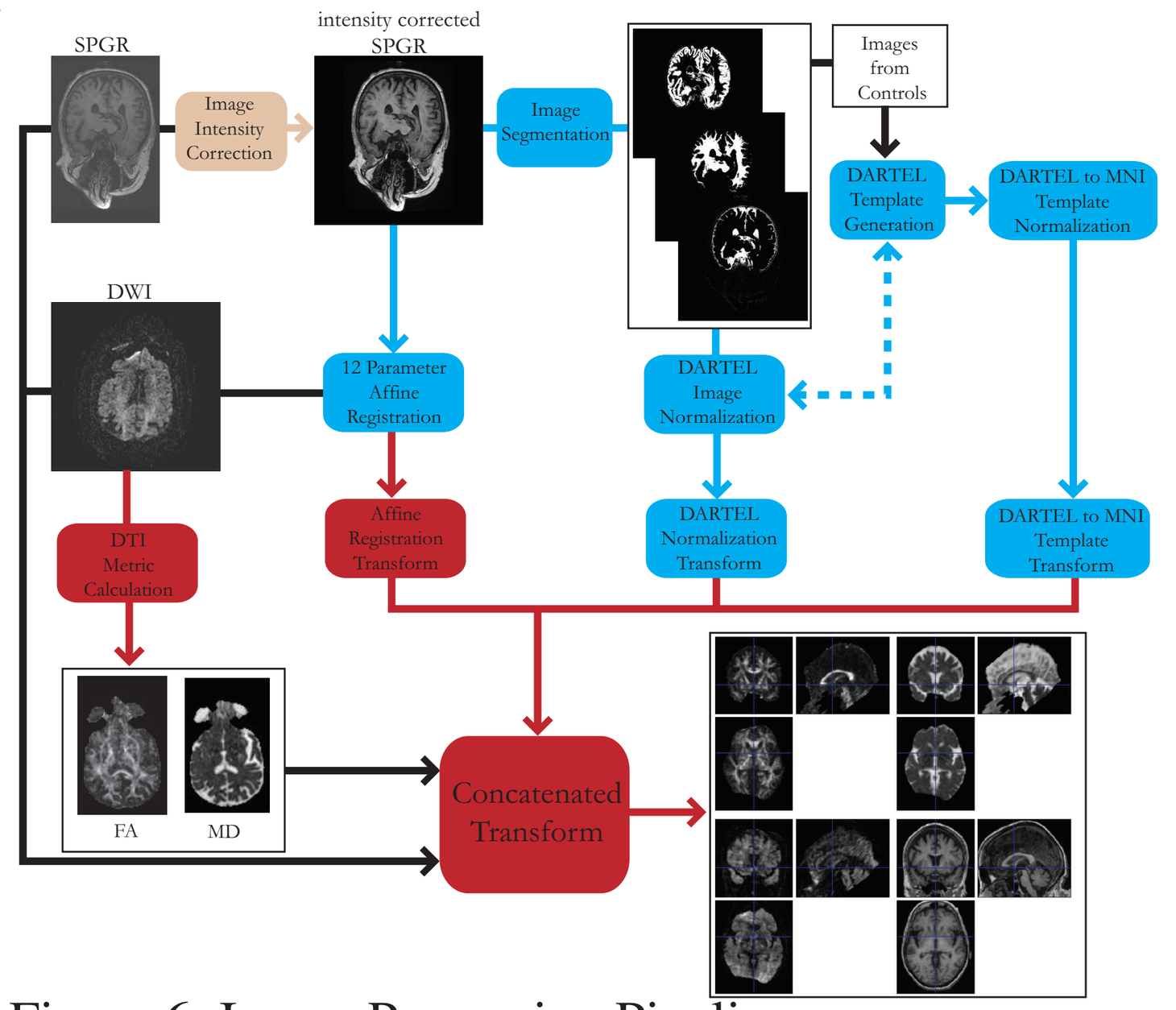
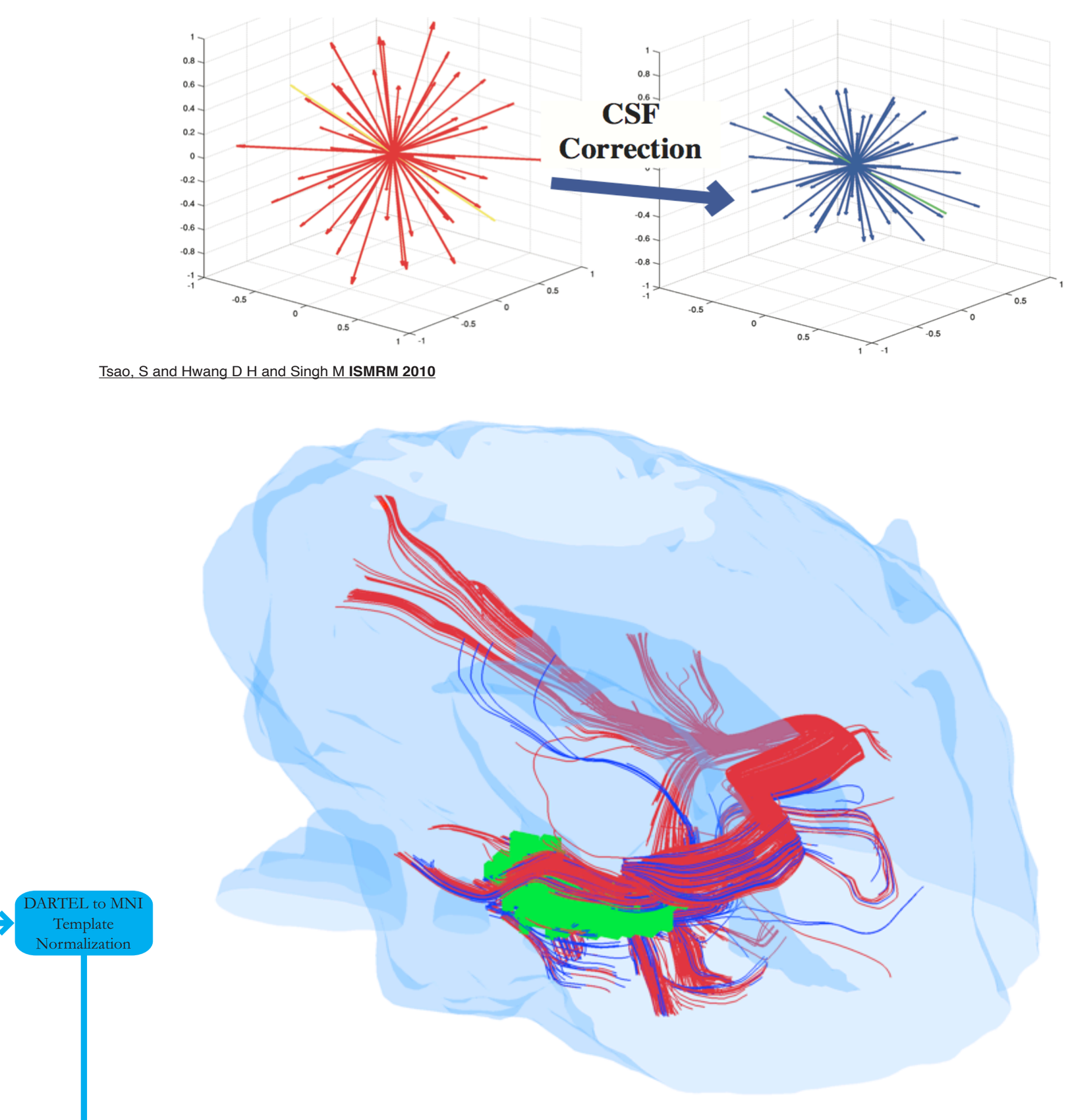


Figure 6: Image Processing Pipeline

$$\frac{S^i}{S_0} = (1 - f_{CSF}) e^{-b\gamma^T D_{Tissue}\gamma} + f_{CSF} e^{-b\gamma^T D_{CSF}\gamma}$$



Sub#	Right Fornix		Left Fornix	
	Corrected FA	Original FA	Corrected FA	Original FA
1	0.4150 ± 0.0372	0.3398 ± 0.0219	0.4428 ± 0.0312	0.3633 ± 0.0210
2	0.2149 ± 0.0182	0.1980 ± 0.0096	0.2801 ± 0.0355	0.2465 ± 0.0170
3	0.2179 ± 0.0344	0.1884 ± 0.0133	0.1997 ± 0.0094	0.1968 ± 0.0058
4	0.2476 ± 0.0370	0.2010 ± 0.0147	0.3175 ± 0.0405	0.2627 ± 0.0227

Figure 5: CSF Compensation Correction

PRELIMINARY RESULTS

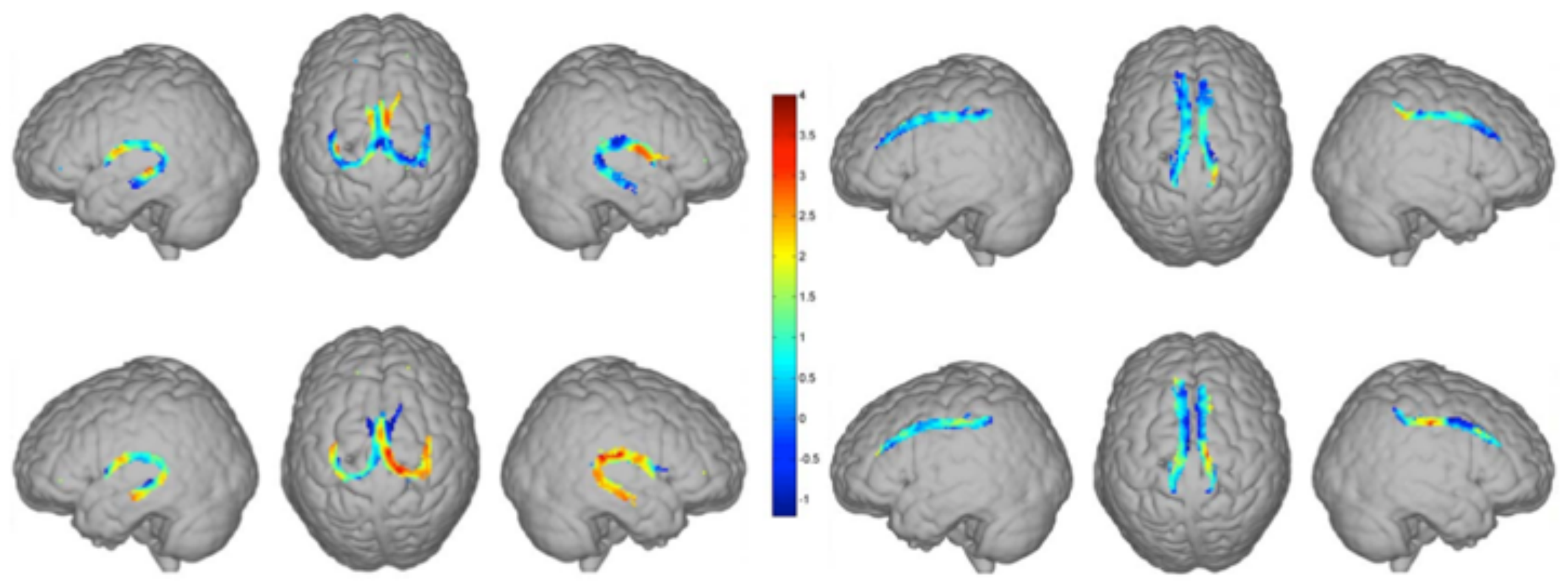


Figure 7: LEFT: Fornix FA t-Score Comparison. MCI > AD (top row) NC > MCI (bottom row). Colors denote the t-score difference between the mean FA of the various populations. RIGHT: Cingulum FA t-Score Comparison. MCI > AD (top row) NC > MCI (bottom row).

SPM8's DARTEL suite provided a much improved normalization of the aged brain populations. Visual inspection of the filtered fornix and cingulum tracts confirmed greatly improved alignment when compared to previous results. The t-score comparisons visually illustrate areas where FA in one population is higher than the other. There appears to be a progressive degeneration of the fornix and the cingulum. The right and left fornix branches both exhibit patterns of damage which begins at the hippocampal end of the fornix and propagates toward the hypothalamus with greater reduction in FA on the right than the left. The cingulum shows less damage, but does appear to be show progressive damage extending to the posterior end, more on the right than left. The complete posterior cingulum portion could not be reliably identified in the common space for all subjects, suggesting a need for further improvement of normalization in AD. These preliminary results shows promise in tracking axonal damage with the progression of Alzheimer Disease. The right greater than left reduction of FA in the fornix and cingulum is consistent with several reports of white matter atrophy and hypometabolism in AD[16].

However, it can also be readily seen that areas that show damage with high T-scores also tend to be areas where there are fiber crossings. We believe that in order to accurate quantify damage in these areas, multi-tensor models should be employed to derive DTI metrics. Our final results can be shown in a manner similar to where maps of the entire tract can be shown and allow us to localize damage in each of them.

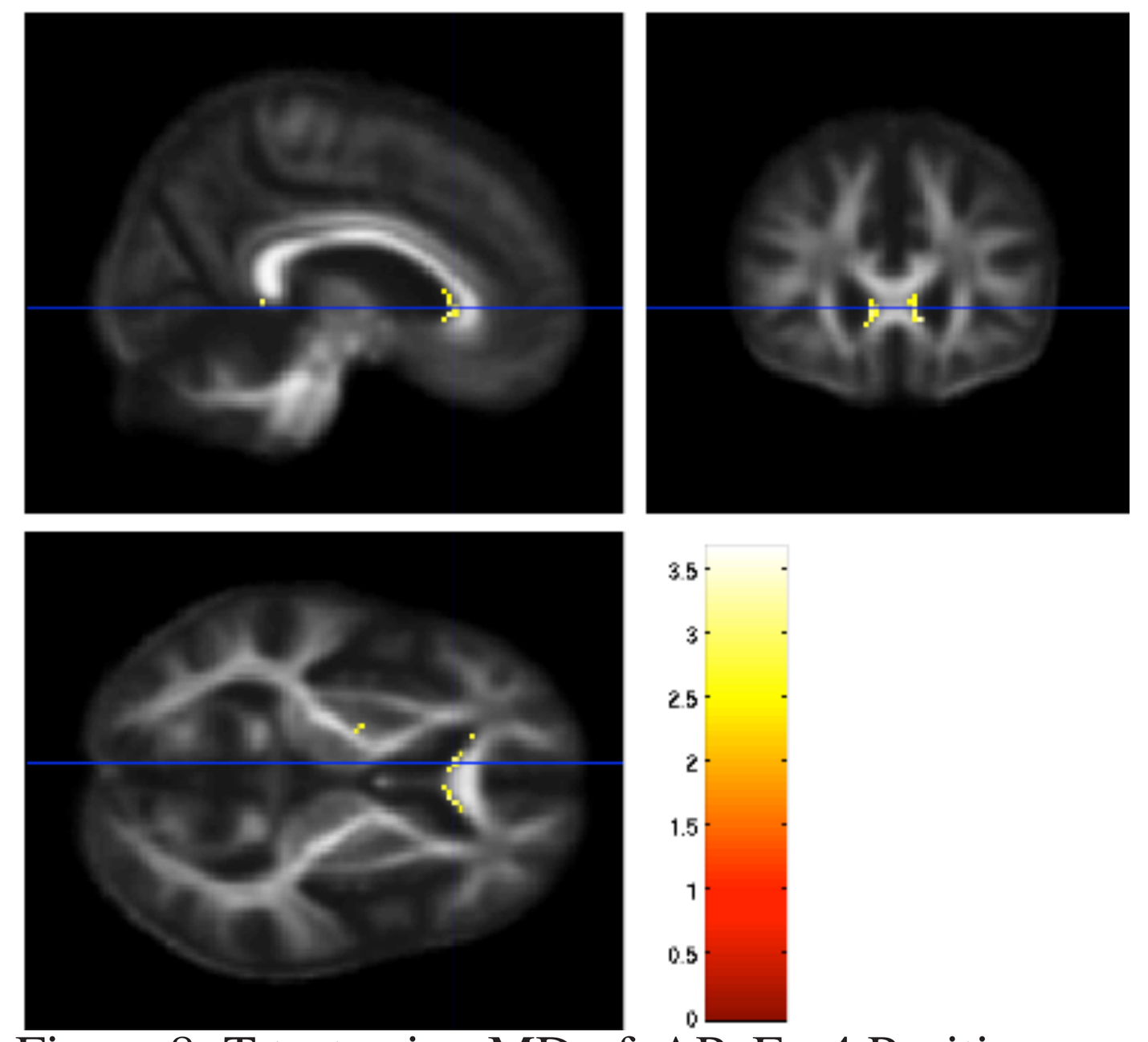


Figure 8: T-test using MD of ApoE-ε4 Positive versus ApoE-ε4 Negative using the ABL Cohort Height Threshold T=2.408 {P<0.01 (unc.)} Extent Threshold k = 5 voxels

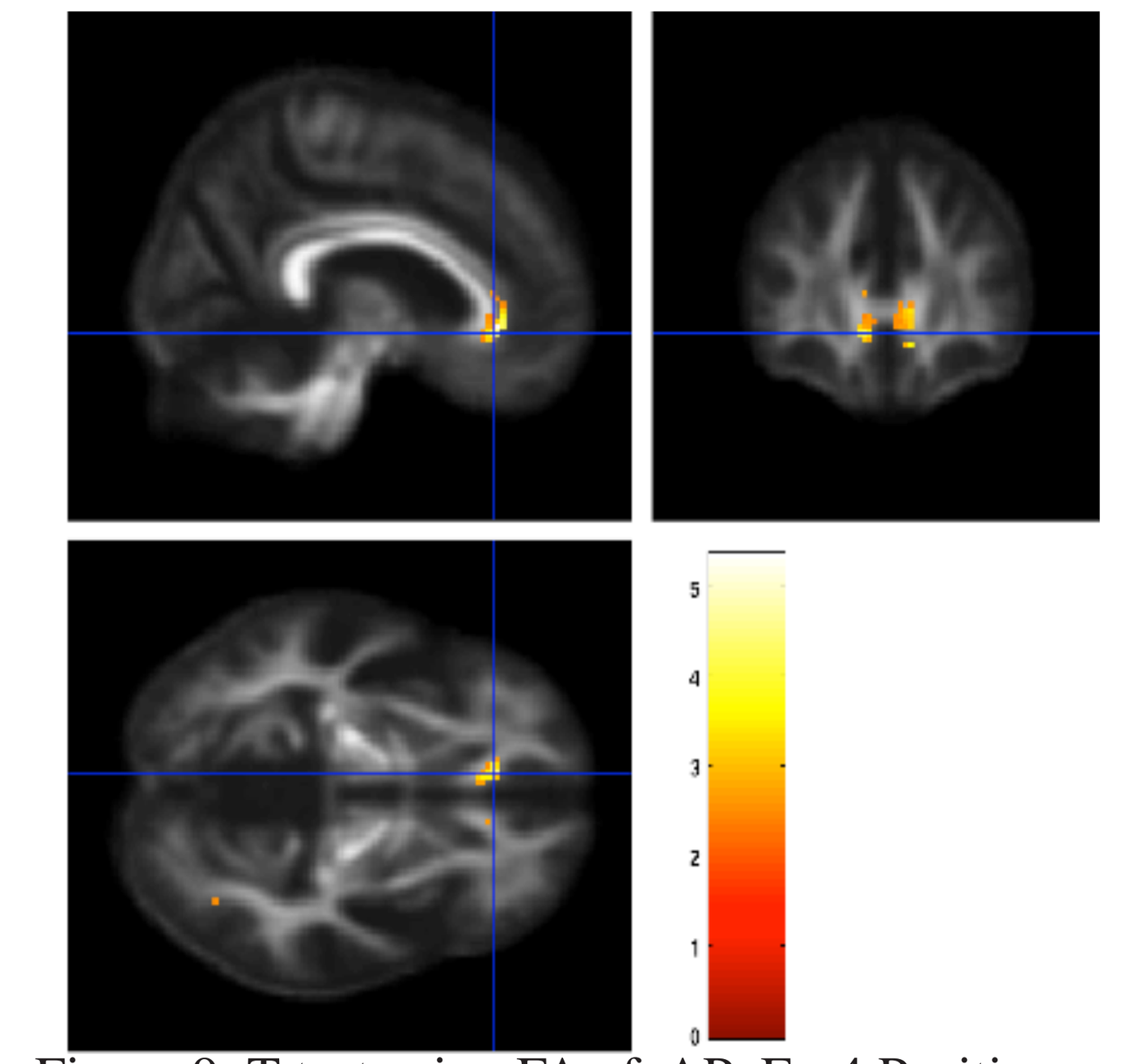


Figure 9: T-test using FA of ApoE-ε4 Positive versus ApoE-ε4 Negative using the ABL Cohort Height Threshold T=2.408 {P<0.01 (unc.)} Extent Threshold k = 5 voxels

These (Fig 8-10) preliminary results show how genetic factors such as EPoE-ε4 can be used to define contrast and ROIs in DTI metrics such as FA and MD. The next step in our analysis is then to differentiate the role of these ROIs in neurodegeneration by relating them back to behavioral scores.

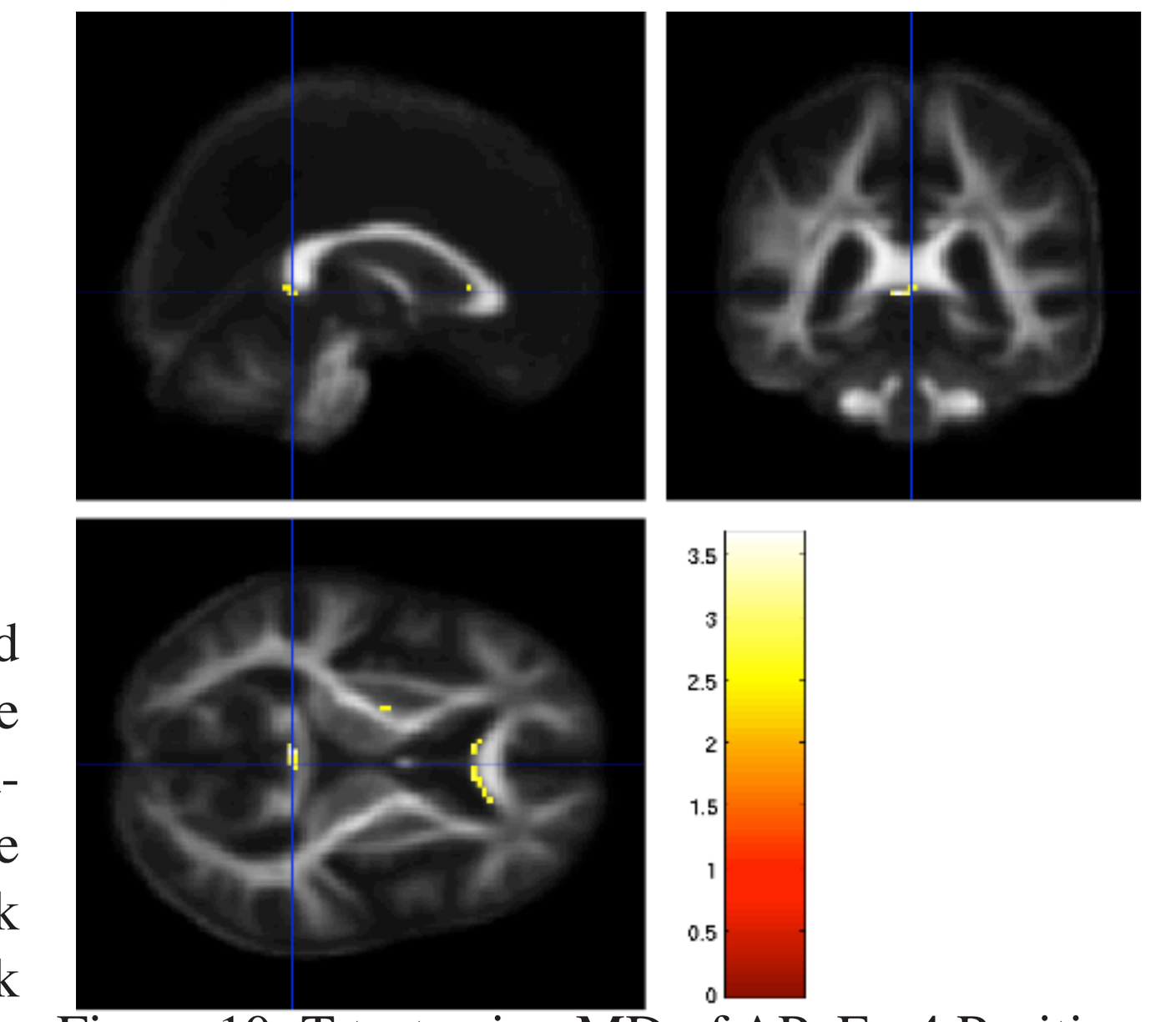


Figure 10: T-test using MD of APoE-ε4 Positive versus APoE-ε4 Negative using the ABL Cohort Height Threshold T=2.408 {P<0.01 (unc.)} Extent Threshold k = 5 voxels

DISCUSSION

The four specific aims will be achieved step-wise and although they can be done separately, the ultimate aim of this work is the design of a tightly integrated group imaging study that will allow us to localize and classify neuronal damage that are related back to behavioral measures. Specific Aims #2 and 3 seek to boost our accuracy in estimating white matter integrity by removing the unwanted CSF component in the diffusion signal as well as using a two tensor model to resolve crossing fibers. The multi-site and multi-scanner aspect of this large-scale study brings its own deficits. In MRI studies, it is difficult to perfectly match harmonization parameters, because unlike other radiological studies such at Computed Tomography (CT), the contrast values are not absolute and do not have definite units. Moreover, each MRI system has significant variations in the artifacts and contrasts it generates. To ensure that our analysis is not biased by these confounds, Specific Aim #4 will allow us to analyze these bias fields within the data and to make the appropriate corrections. By achieving these aims, we hope to improve the sensitivity and specificity of our statistical analysis as specified by Specific Aim # 1, thus allowing us to achieve our penultimate aim of localizing white matter neuronal damage that relates to a specific behavioral characteristic.

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