Comprehensive Autoregional and Autotract based MTR Analysis of Alzheimer's Disease

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Introduction: Studies emphasize a pre-clinical silent phase of Alzheimer's disease (AD) that can last decades before the disease can be detectable by current clinical practice. Reliable, noninvasive imaging techniques that identify disease-related features early and monitor disease progression in the course of AD could prompt therapeutic intervention and slow disease progression. Previous AD neuroimaging studies have shown diffusion tensor abnormalities in gray matter regions including the entorhinal cortex, hippocampus, parahippocampal cortex, and also in white matter tracts like the cingulum fibers(Choo 2010, Clerx 2012). These brain areas seem to correspond with pathological predilection sites that are thought to be susceptible to plaque and tangle deposition in the early stages of AD. The use of quantitative MRI parametric maps such as magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI) maps with mean diffusivity (MD) and fractional anisotropy (FA) has allowed for noninvasive assessment of white matter tract status at a microscopic and macromolecular level. MTR has been shown in pathological studies to be strongly correlated with axonal density and myelination (Fornari 2012). DTI is sensitive to the microstructural organization of axonal fibers in white matter. The tensor information from DTI can be used to reconstruct the white matter fiber tracts of the brain (Fillard 2009). However, a crucial limitation of brain imaging research is the need for operator-dependent manual sampling in various brain regions of interest (ROIs). This procedure causes inter- and intra-operator measurement variations which degrade the utility of longitudinal patient studies, and is labor intensive. Previously, we have developed and validated autoregional methods (Wu et al. 2012, Sidharthan et al. 2012) to provide a precise set of automated imaging tools to analyze specific pathologically relevant structures such as the hippocampus utilizing a broad range of multimodal images. We demonstrate that it is possible to derive autotract specific MTR measurements completely free of operator bias. We performed both autoregional and autotractographical analysis in patients with AD to specifically characterize white matter changes using magnetization transfer imaging. We demonstrate the potential of autoregional and tract-specific MTR as a potential reliable and sensitive imaging marker.

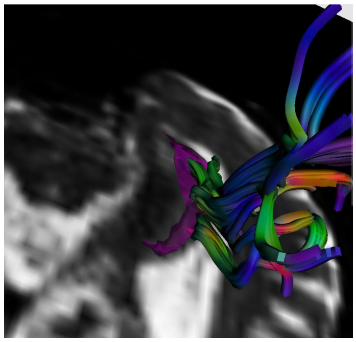

Figure 1: Fiber tracts mapped out using DTI are used to mask out white matter extending from the hippocampus.

Methods and Materials: 17 mild AD (9 males, 8 females, mean age: 75.2 ± 5.5 yrs) and 17 normal aging subjects (7 males, 10 females, mean age: 61.3 ± 4.7yrs) were scanned using a 3 Tesla Siemens system (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany). High-resolution *MT* images were obtained using a three-dimensional gradient echo sequence (TR/TE/FA= 30ms/3.92ms/5°, resolution = 1.0 x1.0 x1.2 mm^3). Images were acquired with and without MT (saturation pulse applied for 9.98 ms with flip angle of 500^o and 1200 Hz offset from water resonance). *DTI* was performed with an echo planar sequence and bandwidth of ±1132 Hz. A b=0 reference image and 13-26 diffusion-weighted images with a b-value of 1000 sec/mm² were acquired at each slice location (TR= 10100ms, resolution = 2.0×2.0×2.0 mm). Automated segmentation was performed on this structural scan using FreeSurfer (Fischl 2012) for ROIs relevant to AD. *Fiber tracking* was performed from the DTI images using software called MedInria (Fillard 2009). The ROIs produced with FreeSurfer were then used in order to limit the fiber bundles and examine the fiber tracts traveling through specific automatically generated regions. These limited fiber bundles were exported as masks which were applied back to the MTR maps for automated tract-based regional analysis. Two tailed t-tests were conducted to detect differences between patient and control groups.

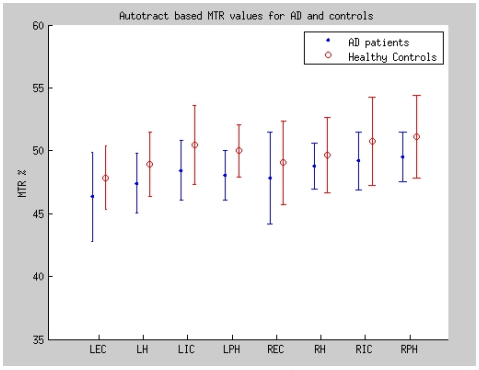

Figure 2: MTR values measured from white matter fiber tracts are reduced in all regions included in this study

Results: MTR values within the fiber tracts included in this study are plotted in Figure 2 with error bars equal to one standard deviation. The table below displays the p-values obtained from t-tests between patient and control groups for both methods. All eight regions included in this study showed improved p-values for the fiber-track based method compared to the original ROI method. The autoregional approach yielded two regions (RPH and LIC) that differed between groups ($p<0.05$), and the autotractography method showed significance in six regions (significant values bolded in table).

MTR p-values comparing patients and controls for autoregional and autotractography methods

	Hippocampus		Entorhinal Cortex		Parahippocampal		Isthmus Cingulate	
	L	R	L	R	L	R	L	R
Autoregional Method	0.121	0.131	0.482	0.4242	0.1765	***0.0354***	***0.0436***	0.0997
Autotractography Method	***0.0105***	***0.0198***	***0.0396***	0.3688	0.1302	***0.0006***	***0.0139***	***0.0316***

Discussion: These automated techniques allow us to conduct standardized analysis across multiple imaging modalities for DTI and MTR obtained on the same brain. This report presents initial cohort study findings based on an objective approach that improves upon an already sensitive method. We have combined automated brain segmentation of 3D neuro-anatomical structures of interest with other strategies (Wu et al. 2012, Sidharthan 2012) that can be used to interrogate the brain at microstructural and macromolecular levels. The addition of DTI fiber tracking with MTR gives a more comprehensive picture of the status of white matter fiber tracts affected by neurodegenerative diseases (Graber 2012). By incorporating tractography into the previously used autoregional MTR method, we have specifically targeted the white matter fiber tracts associated with the reported gray matter regions. The analysis of autotractography expands the already interesting findings in cortical regions and shows additional disease burden along the white matter tracts providing evidence supporting the white matter involvement in AD. These previously unseen changes occur in fiber tracts associated with subcortical regions including the hippocampus, entorhinal cortex, parahippocampal and isthmus cingulate. Since there is no human manual input necessary, our methods can be potentially used as reliable assessment/markers of disease progression for both gray and white matter properties and provide a more thorough analysis and characterization of brain tissue. Neuroimaging studies of predilection sites are crucial for early detection of AD as they are among the first affected brain regions in early stage of AD.

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