

# Decreased Olfactory Tract Fiber Integrity in Mild Cognitive Impairment as Revealed by Diffusion Tensor Imaging

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## PURPOSE:

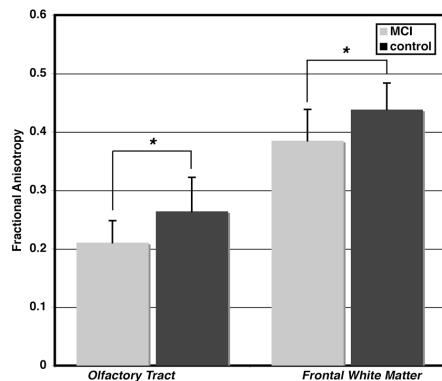
Olfactory deficits have been shown to be an early clinical feature of Alzheimer's disease (AD)<sup>1</sup>. Previously we showed axonal transport rate is decreased in aged rat<sup>2</sup> as well as young mice brains transgenic for AD pathophysiology using manganese enhanced magnetic resonance imaging<sup>3</sup>. Limited investigations have indicated white matter changes in AD that can be distinguished by diffusion tensor imaging (DTI)<sup>4-6</sup>. In this study, we wished to investigate the micro-structural integrity of the olfactory tract in patients with mild cognitive impairment (MCI) using DTI. We hypothesized that MCI subjects would have decreased fractional anisotropy (FA) in the olfactory tract as compared to normal age-matched controls in part reflecting underlying AD pathophysiology.

## MATERIALS AND METHODS:

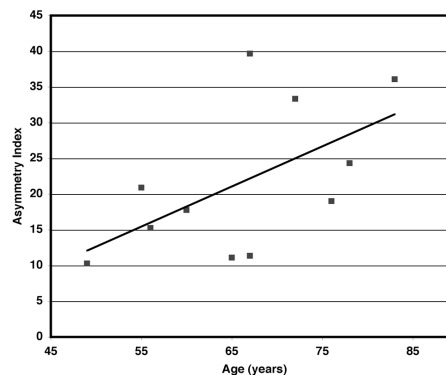
Subjects were recruited as part of a larger study of aging and AD. MCI subjects, determined by Petersen's criteria (n=5, 3 men, age 80.2±6.5 yrs.), and controls (n=9, 5 men, age 75.3±7.5 yrs.) were scanned on a 3T MR scanner (Achieva Dual Quasar gradient system, Philips Medical Systems, Netherlands) and an 8 channel sense head coil. T1-weighted scans, 3D MPRAGE pulse sequence, were acquired using a modified Alzheimer's Disease Neuroimaging Initiative protocol (TR/TE/Flip/ = 6.6ms/3ms/8; 1mm<sup>3</sup> acquired voxel size; inversion time = 850ms; T1 recovery time = 3s; Sense factor of 2 in slice direction). Axial DTI of the whole brain was performed using 32 gradient directions (10mm<sup>3</sup> voxel size, b=1000s/mm<sup>2</sup>, TR/TE/Flip/nex 9.609s/64ms/90/1; sense factor = 2 in phase direction; EPI bandwidth = 1870Hz.). FA maps were generated using DTIstudioV2.30 software (Johns Hopkins Univ., Baltimore, MD) and coregistered with minor non-linear warping to T1-weighted images to standardize image matrices and to correct for potential head motion between scans using automated algorithms (NEUROSTAT, Univ. of Washington, Seattle, WA). Regions of interest (ROIs) were placed in the olfactory tract (OT) and in the frontal white matter (FWM) in the cortex on T1-weighted coronal images and values on coregistered FA maps were measured. Average FA values for both right and left olfactory tracts of MCI versus controls were compared using a student's t-test (p<0.05). Asymmetry index between right and left OT ROIs was calculated as  $AI = |(r-l)/(r+l)| * 100$ .

## RESULTS:

Group averaged FA values for ROIs in the olfactory tract were decreased significantly in MCI patients compared to controls. Due to considerable asymmetry in many subjects (both MCI and controls), lowest FA value, either right or left was compared across subjects (FA<sub>least</sub> = 0.17±0.03 and 0.02±0.03 for MCI and controls, respectively). After averaging right and left tract ROIs, difference in FA values remained significant (FA<sub>average</sub> = 0.21±0.04 and 0.26±0.06 for MCI and Controls respectively) (Figure 1). FA values in the frontal white matter were decreased in MCI versus control subjects (FA = 0.39±0.05 and 0.44±0.05 for MCI and controls respectively). Asymmetry was observed in some, but not all cases both MCI and control. Of control subjects showing 10% or greater asymmetry in FA values of the left and right olfactory tract, there was a positively correlated age-related increase (r=0.62) (Figure 2).



**Figure 1: Group-wise comparison of FA values.** ROI analysis in olfactory tract (average right and left) and frontal white matter indicated decreased FA in both regions in MCI versus control subjects (p<0.05)



**Figure 2: Asymmetry index increases with age in normal subjects.** In controls (n=12) with asymmetry between right and left FA values in the olfactory tract, % asymmetry increased with age.

## SUMMARY AND CONCLUSIONS:

This study indicates that white matter integrity as assessed by fractional anisotropy in the olfactory tract as well as frontal white matter is decreased in MCI patients. As far as we know, this is the first study to show dysintegrity of the olfactory tract in MCI patients. Reductions in cerebral white matter FA values are consistent with some of previous investigations of AD and MCI patients. Increased asymmetry with aging may be an indication of progressive dysintegrity of the olfactory tract, the findings similar to those often seen in neurodegenerative processes. Our previous findings of olfactory axonal transport deficits in rodents and reported clinical deficits with olfactory function in AD are consistent with the current findings of DTI analysis. These findings may have important implications as to AD pathophysiology that has been overlooked previously.

**REFERENCES:** 1. Attems, J. and K.A. Jellinger, Olfactory tau pathology in Alzheimer disease and mild cognitive impairment. *Clin Neuropathol*, 2006. 25(6): p. 265-71. 2. Cross, D.J., J.A. Flexman, Y. Anzai, et al., Age-related decrease in axonal transport measured by MR imaging in vivo. *NeuroImage*. In Press, Accepted Manuscript. 3. Cross, D.J., J.A. Flexman, Y. Anzai, et al. In Vivo MRI Investigation of Decreased neuronal Transport with Aging and in Brains Expressing Alzheimer's Pathology. in *International Society of Magnetic Resonance in Medicine*. 2007. Berlin, Germany. 4. Head, D., R.L. Buckner, J.S. Shimony, et al., Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. *Cereb Cortex*, 2004. 14(4): p. 410-23 5. Kantarci, K., R.C. Petersen, B.F. Boeve, et al., DWI predicts future progression to Alzheimer disease in amnesic mild cognitive impairment. *Neurology*, 2005. 64(5): p. 902-4. 6. Zhang, Y., N. Schuff, G.H. Jahng, et al., Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology*, 2007. 68(1): p. 13-9.