Combined DTI and cognitive measures for detection of early Alzheimer's disease

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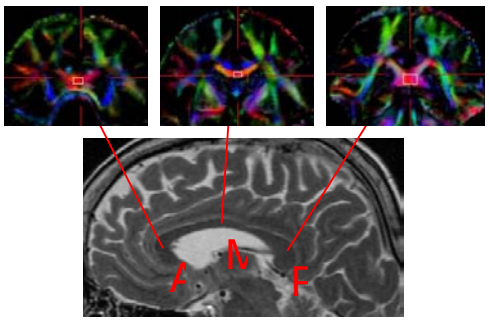
Synopsis
We have developed a two-stage concurrent inhibition model which predicts that AD patients lack proper connectivity between perceptual and mnemonic modules. We tested this prediction by using DTI to measure integrity of corpus callosum. AD patients showed significantly decreased fractional anisotropy (FA) values in WM in the anterior and posterior corpus callosum. FA values from posterior corpus callosum correlated with several cognitive measures. Overall, the results indicate a strong link of cognitive and attentional impairments to WM changes in early AD. Results also provide additional evidence of relevant pathways connecting brain structures involved in cognitive processing.

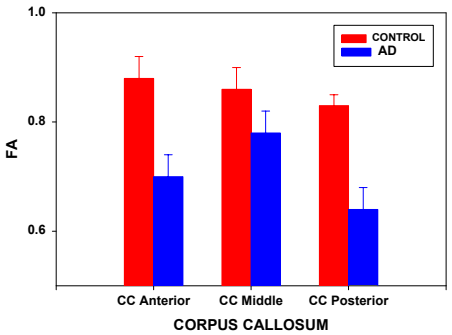
Introduction
Alzheimer's disease (AD), a neurodegenerative disorder associated with progressive functional decline, is initially diagnosed as a memory disorder accompanied by attentional and perceptual deficits. Perceptual deficits in early AD include impaired visual motion processing with elevated thresholds for optic flow, the patterned visual motion seen during an observer self-movement (1). Attentional deficits in early AD include more "attentional blink" errors (i.e., decrease recognition of two targets, embedded in a string of distractors, when the two targets are presented in close temporal proximity ~ 550 msec) lasting over longer period (2). Based on the above findings, we developed a 2-stage concurrent inhibition model which can explain such impairments (2). The central feature of the model is a memory mechanism providing feedback control of input to category specific perceptual processors. This model predicts that an important source of impairment in visual processing is compromised feedback connections from the memory system to the initial perceptual processors. In this work, we present the pilot findings using DTI for evaluation of the integrity of corpus callosum (CC), the main white matter tract connecting the two cerebral hemispheres.

Method
To date, we have performed DTI and neuropsychological testing with 10 subjects: five AD patients (mean age = 75.4 years, mean MMSE = 21 with range 19 - 24) and five age-matched elderly normal controls (mean age = 75.6 years, mean MMSE = 29 with range 27 - 30).
Neuropsychological evaluation: Neuropsychological tests for evaluation of basic cognitive capacities included: 1) The Mini-Mental Status Examination as a measure of overall impairment in AD; 2) The Road Map test was used to assess topographic orientation in simulated route following; 3) Two subtests from the Wechsler Memory scale were used: the Verbal Paired Associates test was used to assess immediate and delayed verbal memory, and the Figural Memory test was used to assess immediate visual recognition; 4) The Category Name Retrieval test to assess memory retrieval and cognitive flexibility; 5) The Judgement of Line Orientation test to test the ability to judge angular relationships; 6) The Facial Recognition test to assess visuospatial processing.
DTI protocol: MRI examinations were performed on a GE Signa 1.5 T MR scanner. In addition to conventional anatomic images, coronal DTI imaging with a single-shot pulsed-gradient spin-echo (PGSE) EPI were performed. Diffusion weighting were applied in 20 different orientations with b value = 0 and 1000 s/mm2. Images cover anatomic structures including the WM subcortical bilateral frontal and posterioparietala areas, fronto-postrioparietal supperior bundles, bilateral anterior and posterior cingulum, and the anterior (genu) and posterior (splenium) portion of CC.

Results
Despite small sample size, the results indicate that there is statistically significant difference between AD patients and age-matched controls. The mean FA values, obtained with 5 AD patients and 5 age-matched controls, are presented in Fig 2 for the CC. AD patients showed smaller FA values than age-matched controls at the anterior (p = .02) and posterior (p = .003). There were also statistically significant positive correlations between FA values from the posterior CC and performance on several neuropsychological tests indicating that better performance on the test was correlated with higher integrity of white matter. For control group there was significant correlation between FA and Road test (r = .96, p = .01), while for AD group there was significant correlation with test of Category Name Retrieval test (r = .99, p = .001) (Fig 3) and the Judgement of Line Orientation test (r = .91, p = .03). Discriminant function analysis showed 100 % accuracy in differentiating AD patients from normal aging when we combined structural (FA measurements) and performance (test scores from neuropsychological tests) data.

Discussion
Our pilot results obtained with only 5 AD patients and 5 controls showed that DTI can reliably differentiate between mildly impaired AD patients and age-matched elderly controls. In addition, the pilot results show that the DTI measure parameter FA, especially from the posterior CC, has the necessary sensitivity to indicate the relationship between WM integrity and cognitive performance on some standard neuropsychological tests. Combination of neuroanatomical and performance data can unmistakenly detect an AD patient from normal elderly. Our initial pilot results are, thus, encouraging and promising in that with combining neuroanatomical and behavioral methods we may be able to reliably distinguish AD from normal aging at a relatively early stage. After all, successful treatments of AD will require reliable and sensitive diagnostic procedures for early detection and therapeutic monitoring of the disease.





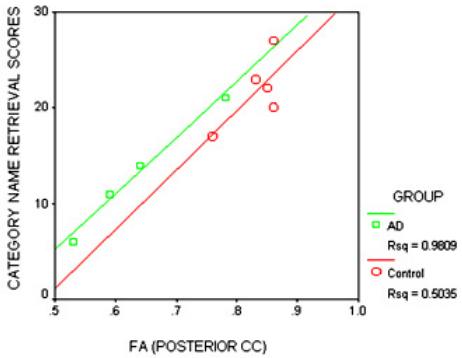


Fig 1 (left). ROIs at anterior (A), middle (M), and posterior (P) sites of corpus callosum from which FA values were obtained. Rectangle from three sites approximates the ROI sizes. Fig 2 (middle). Mean FA values for Control and AD groups for the corpus callosum at the anterior, middle, and posterior sites. Fig 3 (right). Scatter diagram illustrating the relationship between FA values at posterior CC and Category Name Retrieval test scores for AD and age-matched control groups.

Reference: (1) Tetewsky,S, Duffy C. J, Neurology, 52, 958-965 (1999). (2) Kavcic V., Duffy C.J., Brain, 126,1173-1181 (2003)