FMRI in the Diagnosis of Early Alzheimer's Disease

M.M. Machulda, H.A. Ward, B. Borowski, C.R. Jack, Jr.
Mayo Clinic, Rochester, MN, USA

Abstract
The purpose of this study was to determine whether an FMRI memory task distinguishes among patients with mild cognitive impairment (MCI), patients with mild Alzheimer's Disease (AD), and cognitively normal elderly controls. Pathologic progression of AD begins in the medial temporal lobe, which supports declarative memory function. Twenty-four subjects (9 controls, 9 MCI, 6 AD) completed an FMRI complex scene-encoding task. ROC analyses revealed that medial temporal lobe activation in subjects with MCI was intermediate between that of controls and early AD, but considerable overlap was observed among the groups. The results are consistent with findings from other MRI modalities.

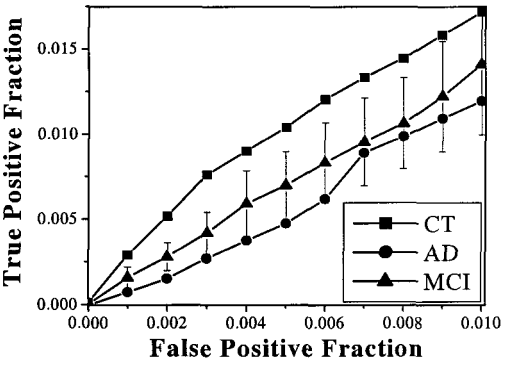
Methods
24 subjects from the Mayo Alzheimer's Disease Research Center were studied: 9 cognitively normal subjects, 9 patients with MCI [1], and 6 with very mild AD. The activation paradigm (complex scene encoding) consisted of cyclic presentations of novel pictures. The subjects were asked to carefully memorize each picture and were instructed that they would later be tested on recall of these pictures. The foil portion of the task consisted of a pixilated image in which one of the pictures had undergone a randomized reshuffling and the original picture was not recognizable. At the completion of the FMRI examination, each subject was tested for free recall of the images shown during the FMRI task.

Scanning Parameters
Whole brain asymmetric spin-echo, echo planar FMRI (TR=2750, TE = 50 msec, FOV 24 cm, 64x64 matrix) was performed using a 3.0T scanner. Twenty-six contiguous 5 mm axial slices provided coverage of the entire brain. Each FMRI run consisted of 4 cycles of the encoding task (21 sec) alternated with 4 cycles of the foil task (21 sec). An SPGR anatomic reference scan was also acquired on each subject.

The data were analyzed with an ROC (Receiver Operating Characteristic) method. Two anatomically defined ROIs (Region of Interest) were selected to fulfill the criteria necessary to perform an ROC analysis. Medial temporal lobe ROIs, which included the hippocampus and parahippocampal gyri, demarcated true positive activation. A second ("false positive") ROI encompassed the frontal lobe on three coronal slices posterior to the anterior commissure.

Results
The ROC curves were analyzed over the false positive activation range of 0 to 1%. Across this range of false positive activation, true positive medial temporal lobe activation was greatest in the controls and least in the AD subjects. That is, the ROC curve of the control group was located to the left of both the MCI and AD group, indicating greater medial temporal lobe activation at a given false positive fraction value in controls than AD. On average, MCIs were located between controls and ADs.

Because of inter-group overlap, SEM error bars were placed only for the MCI group for clarity of presentation. (See Fig.)



Discussion
1. Medial temporal lobe activation can be obtained with a complex scene-encoding paradigm in cognitive normal elderly subjects, patients with MCI, and patients with early AD.
2. Medial temporal lobe activation was greater in cognitively normal controls than in AD patients.
3. Medial temporal lobe activation in subjects with MCI was intermediate between that of controls and AD subjects. This intermediate position of MCI subjects in the FMRI task matches the relative cognitive performance of the three groups on a free recall task at the end of the FMRI study. The relative ranking of the three clinical groups by FMRI performance also matches results from studies of other MRI modalities [2-5]. Specifically, brain morphometric measurements of MCI subjects fall in between those of control and AD subjects [2,3]. The same is true of ^{1}H MRS measurements and apparent diffusion measurements [4,5]. Our FMRI data support the notion that FMRI activation measurements, like measurements derived from other MRI modalities, are sensitive to the early cognitive impairment seen in individuals who qualify for a clinical diagnosis of MCI.
4. Although the mean group performance of controls, MCIs, and ADs were different, considerable overlap was observed among individual in the three groups.

References
1. Petersen, R., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., *Arch Neurol.*, 56, 303, 1999.
2. Xu, Y.C., Jack, C.R., O'Brien, P.C., Kokmen, E., Smith, G.E., Ivnik, R.J., Boeve, B.F., Tangalos, E.G., Petersen, R.C., *Neurol.* 54, 1760, 2000.
3. Jack, C.R., Petersen, R.C., Xu, Y.C., O'Brien, P.C., Smith, G.E., Ivnik R.J., Boeve, B.F., Tangalos, E.G., Kokmen, E., *Neurol.* 55, 484, 2000.
4. Kantarci, K., Jack, C.R., Xu, Y.C., Campeau, N.G., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Kokmen, E., Tangalos, E.G., Petersen, R.C. *Neurol.*, 55, 210, 2000.
5. Kantarci, K., Jack, C.R., Xu, Y.C., Campeau, N.G., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Kokmen, E., Tangalos, E.G., Petersen, R.C., *Radiol.*, 219, 101, 2001.

Acknowledgments This research was supported by NIH grants AG19142, AG16574, and AG06786.