Identification of Alzheimer Disease Risk by Functional Magnetic Resonance Imaging

Adam S. Fleisher, MD; Wes S. Houston, PhD; Lisa T. Eyler, PhD; Susan Frye, APRN, BC; Cecily Jenkins, PhD; Leon J. Thal, MD; Mark W. Bondi, PhD

Background: Functional magnetic resonance imaging plays a promising role in the preclinical characterization of Alzheimer disease (AD) for use in early diagnosis and in preventive drug trials.

Objective: To determine whether functional magnetic resonance imaging can reliably distinguish risk groups for AD among cognitively normal middle-aged adults.

Design: Cross-sectional case-control study.

Setting: University of California, San Diego, Alzheimer Disease Research Center participants and San Diego community volunteers.

Participants: Twenty cognitively normal individuals (10 high risk and 10 low risk), aged 58 to 65 years, were divided into 2 groups based on the presence or absence of the apolipoprotein E ε4 allele and a positive family history of AD.

Main Outcome Measures: Word pairs were presented in a blocked design alternating between conditions of novel pairs, repeated pairs, and fixation. Whole-brain differences in blood oxygenation level–dependent brain responses between conditions were compared across risk groups.

Results: Compared with the low-risk group, the high-risk group showed many areas of differential blood oxygenation level–dependent response in regions commonly associated with AD pathology (eg, the left medial temporal lobe). Furthermore, different patterns of association between left medial temporal lobe activity and memory performance were demonstrated.

Conclusions: Results support a theory of upregulation in neuronal memory systems in people at risk for AD many years before the typical age at disease onset. They further demonstrate that functional magnetic resonance imaging is a viable technique to identify persons at risk for AD.

Arch Neurol. 2005;62:1881-1888

RESULTS OF IMAGING STUDIES1-6 suggest that nondemented older adults at increased risk for Alzheimer disease (AD) have alterations in memory-related brain activity and that these changes appear to occur in brain regions associated with the clinical manifestations of AD. There is also evidence that functional MR imaging (fMR imaging) can be used to detect preclinical susceptibility to AD. For example, upsurges in blood oxygenation level–dependent (BOLD) signal in the medial temporal lobes (MTLs) of nondemented older adults at increased genetic risk for AD (based on the presence of apolipoprotein E ε4 [APOE ε4] alleles) have been reported.4,5 Bookheimer et al5 first demonstrated this effect using a verbal paired associative learning task, although the subjects in their study had a wide age range of 46 to 71 years, and subjects who were carriers of the APOE ε4 allele had worse delayed recall memory scores compared with subjects who were homozygous for APOE ε3. More recently, using a nonassociative picture-encoding task, Bondi et al6 demonstrated increased MTL BOLD signal in APOE ε4 carriers compared with APOE ε3 carriers among subjects with intact memory functioning in their eighth decade of life.

For fMR imaging findings to be useful as a biomarker of preclinical disease, it is important to standardize, validate, and optimize these techniques. We must also determine if these findings occur in younger individuals before the clinical manifestations of dementia are present, as has been shown with positron emission tomography.3 The present study sought to demonstrate whether BOLD fMR imaging reliably distinguishes risk groups for AD. Given the recent positron emission tomography finding by Reiman et al3 of glucose metabolic reductions in young adults at increased genetic susceptibility for AD, we examined whether such changes were also apparent using fMR imaging. Therefore, we performed an fMR imaging study.
of verbal associative encoding among younger at-risk subjects with narrower age ranges than those previously described. In addition, we loaded more heavily on risk by requiring APOE ε4-positive subjects to also have a positive family history for dementia. Overall, to further develop fMR imaging for use as a potential biomarker in preclinical AD, we sought to extend previous findings to younger subjects to examine for differential brain response.

### METHODS

#### SUBJECTS

Twenty subjects were recruited from an ongoing longitudinal study at the University of California, San Diego, Alzheimer Disease Research Center (n = 6) and from the San Diego community (n = 14). Subjects were separated into 2 risk categories defined by the presence (high-risk group) or absence (low-risk group) of both the APOE ε4 and a positive family history of late-onset dementia in a first-degree relative. Thirty-three potential right-handed subjects between the ages of 55 and 65 years were identified, 20 of whom (age range, 58-65 years) were selected based on demographic matching. This study was approved by the University of California, San Diego, Human Research Protection Program, and written informed consent was obtained from all participants. The high-risk group consisted of 9 APOE ε3/ε4 heterozygotes and 1 APOE ε4/ε4 homozygote, all with positive family histories of late-onset dementia. The low-risk group consisted of 10 APOE ε3/ε3 homozygotes, all with negative family histories of late-onset dementia. All participants were evaluated to determine that there were no significant medical or psychiatric conditions that would affect cognition. Subjects with active cardiac or cerebrovascular disease were excluded. All participants had normal findings on physical and neurological examinations performed by a board-certified neurologist (A.S.F.), and structural MR images were screened to exclude subjects with infarctions, excessive subcortical vascular disease, or space-occupying lesions.

#### NEUROPSYCHOLOGICAL ASSESSMENT

Global measures of cognition included the Mattis Dementia Rating Scale and the Folstein Mini-Mental State Examination. Other tests included the California Verbal Learning Test (CVLT), phrase recall from the Blessed Information-Memory-Concentration Test, Boston Naming Test (30-item version), Verbal Fluency, Trail-Making Test, and Clock Drawing. Tests were administered to all subjects within 1 month of fMR imaging (Table 1).

#### fMR IMAGING BEHAVIORAL TASK

A verbal paired associative encoding task was used in a blocked design consisting of novel word pairs (4 blocks), repeated word pairs (4 blocks), and fixation to a central crosshair (8 blocks) presented in pseudorandom order. While lying in the fMR imaging scanner and before fMR imaging, participants viewed 16 pairs of associated nouns (eg, bed-BUG) back-projected on a screen at the subject’s feet until 10 (63%) of 16 pairs could be recalled successfully. The active task was then administered during fMR imaging with each stimulus block containing 4 word pairs displayed for 5 seconds each. Stimulus blocks were separated by fixation trials lasting 8, 12, or 16 seconds. Participants were asked to learn each pair for subsequent cued recall testing. To assess attention to the task, participants were asked to indicate on each trial which of the 2 words was capitalized by pressing 1 of 2 buttons. After fMR imaging, we assessed cued recall by presenting the first word in each pair and requiring verbal responses for the associated word. Each participant completed 2 runs of the paired associative task, separated by about 12 minutes, during which time a high-resolution anatomical MR image was collected. Recall was tested after each run. A unique set of words was used for each run.

#### IMAGE ACQUISITION

Participants were imaged using a Magnetom 1.5-T magnet (Siemens AG, Munich, Germany). The BOLD response during the tasks was assessed with gradient recalled echo-planar...
imaging sequences (69 whole-brain images of 32 axial sections; 4-mm thickness; 4 × 4-mm in-plane resolution; repetition time, 4000 milliseconds; echo time, 40 milliseconds; and flip angle, 90°). Anatomical images were acquired using a magnetization-prepared rapid acquisition gradient echo protocol (sagittal sections; 1-mm thickness; 1 × 1-mm in-plane resolution; repetition time, 11.4 milliseconds; echo time, 4.4 milliseconds; and flip angle, 10°).

IMAGE ANALYSIS

Structural and functional images were analyzed using the AFNI software package for analysis and visualization of functional magnetic resonance neuroimages. Using a 3-dimensional iterated, linearized, weighted least squares method with Fourier interpolation, echo-planar images were motion corrected across time points to the most typical base image. Time points with isolated head movements not corrected by the registration algorithm (3DVolreg) were removed from statistical analysis. The motion-corrected BOLD signal intensities were then used as dependent variables in a multiple regression analysis using the program 3DDeconvolve. The magnitude of the fit coefficient for the general linear contrast in signal intensity between novel and repeated word pairs at each voxel was used as the dependent variable for group analyses. Fit coefficient maps were then transformed into standardized Talairach and Tournoux atlas space and blurred with an 8-mm, full-width at half maximum gaussian filter. The effect of group and the interaction of group × run on the magnitude of the novel vs repeated and novel vs fixation contrasts were then assessed in each voxel using an analysis of variance with group and run as fixed effects and with participant as a random effect.

In a whole-brain analysis, follow-up t tests were used to explore significant main effects and interactions identified from the analyses of variance. Significant cluster size was determined using a Monte Carlo simulation program (AlphaSim), with a cumulative proportion criterion of less than .05. For the whole-brain analysis, this equated to a cluster volume of 22 voxels (ie, 1408-mm³ volume), protecting the hypothesis that chance volume activations occur less than 5% of the time when no activation is present.

Two regions of interest (ROIs) consisting of the right and left hippocampus and parahippocampus were used for further analyses. These ROIs were defined using AFNI Talairach Daemon software. They were generated on an averaged anatomical image of all 20 subjects that had been warped into standard Talairach and Tournoux space. This standard ROI mask was then overlaid onto each subject's anatomical image and visually inspected to ensure significant overlap with the anatomical structures of interest. Clusters of brain response were considered significantly different from 0 within groups or significantly different between the 2 groups if they contained at least 9 contiguous voxels, each with a threshold of P = .03 (ie, 576-mm³ volume). For the statistical maps of brain response presented in Figure 1 and Figure 2, the magnitude of between-group or within-group effect was expressed as $\eta^2$ and was dichotomized based on the direction of the effect (range, −1.0 to 1.0). Consistent with prior work, correlational and control analyses were done to assist in interpretation of between-group differences.

CORRELATION ANALYSIS

Correlations between voxelwise BOLD activations and performance on the recall task after fMR imaging, as well as on word
list learning as measured by the CVLT (list A trials 1-5 total recall), were computed. This was done for MTL ROIs that showed significant between-group BOLD differences. The AFNI program 3DRegana calculated linear regression analyses using individual subject memory test performance and single-voxel BOLD coefficients within the ROI. This was done independently for each subject group for the novel vs repeated contrast compared with fixation.

CONTROL ANALYSIS

The novel vs fixation contrast was used to compare between-group BOLD signal in a control region (primary visual cortex, Brodmann area 17) in which the contribution to the associative encoding task was not expected to differ between groups. This was done to explore the specificity of observed group dif-

Figure 2. Region of interest (ROI) analysis showing clusters of significant differences in blood oxygenation level–dependent signal for the novel vs fixation contrast overlaid onto 2-dimensional sagittal, axial, and coronal sections of an averaged anatomical image of all 20 subjects in Talairach and Tournoux space. Activations shown include voxels significant at $P = .05$ that are contained within a left hippocampal or parahippocampal anatomical ROI with a cluster of 13 or more contiguous voxels (ROI criterion). The color scale represents effect sizes for the between-group differences as measured by $t$. A, Low-risk within-group analysis. B, High-risk within-group analysis. C, High-risk vs low-risk between-group analysis. R indicates right; L, left.

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ficients for this contrast and to examine whether broad underlying physiological factors may affect between-group findings. The methods used for this analysis were identical to those used for the primary ROI analyses.

RESULTS

DEMOGRAPHICS

There were no significant group differences in age, education, sex, cognitive test scores, or cued recall scores after fMR imaging. Characteristics of the cohort are given in Table 1.

WHOLE-BRAIN ANALYSES

Within-Group Analysis

During the novel vs repeated contrast, significant areas of increased BOLD signal (novel > repeated) were observed in the low-risk group in the right anterior cingulate region, left posterior middle temporal gyrus, left anteroinferior frontal region, left middle frontal gyri, left lenticular nucleus, and bilateral mediofrontal regions. Significant decreases (repeated > novel) occurred in the right superotemporal gyrus, right posterior cingulate region, and right anterosuperior frontal region (Figure 1A). Both groups demonstrated significant bilateral parahippocampal activation during novel word pair encoding compared with fixation (novel > fixation). The only significant parahippocampal activity during the novel vs repeated contrast was seen on the left side in the high-risk group (Figure 1B).

Between-Group Analysis

Relative to the low-risk group, the high-risk group demonstrated significantly increased BOLD signal during novel vs repeated word pair encoding in the right posterior middle temporal area, right cerebellar vermis, left lingual area, bilateral anterior cingulate region, and right anterofrontal region. Relative to the high-risk group, the low-risk group showed clusters of increased signal in the right anterofrontal region, posterior cingulate region, and right middle frontal area (Figure 1C). Significant cluster location, volume, mean effect size, and direction of signal change for each group (novel > repeated or repeated > novel) are given in Table 2.

Whole-brain analysis of the novel vs fixation contrast demonstrated a greater number of cluster activations representing differences between the two risk groups (Table 3). The most notable difference in the results of this analysis was the significantly increased activity during novel word pair encoding in the left posterior parahippocampal region in the high-risk group compared with the low-risk group.

ROI ANALYSES

Evaluation of the right and left hippocampal and parahippocampal ROIs (Figure 2) revealed between-group left parahippocampal differences in activity (high risk > low risk) in the novel vs fixation contrast (P < .05). No significant group differences were found for the novel vs repeated contrast in these regions. No significant clusters were demonstrated for either contrast in the right ROI.

POST HOC ANALYSES

Correlational Analysis

In the left MTL ROI, the low-risk group demonstrated a positive correlation between mean fit coefficients during novel encoding (ie, novel vs fixation) and CVLT learning performance (low-risk group r = 0.91, r² = 0.83, P < .001), whereas the high-risk group did not (high-risk group r = −0.37, r² = 0.11, P = .30) (Figure 3A). Neither group showed significant correlations between repeated word pair encoding (ie, repeated vs fixation) and

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Table 2. Regions of Significant Group Differences in Blood Oxygenation Level-Dependent (BOLD) Signal Between the High-Risk and Low-Risk Groups During Presentation of Novel vs Repeated Word Pairs

<table>
<thead>
<tr>
<th>Brain Region*</th>
<th>Volume, mm³</th>
<th>V² for High vs Low Risk</th>
<th>Direction of Within-Group Activations†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low Risk</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Low Risk</td>
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<tr>
<td></td>
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<td>Repeated &gt; novel</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Novel &gt; repeated</td>
</tr>
</tbody>
</table>

Abbreviations: A, anterior; B, bilateral; I, inferior; L, left; P, posterior; R, right; S, superior.

* Talairach and Tournoux's coordinates are given in parentheses.
† Novel > repeated indicates a relative increase in within-group BOLD signal for this contrast. Repeated > novel indicates a relative decrease in within-group BOLD signal for this contrast.
CVLT scores (low-risk group $r=0.4$, $r^2=0.16$, $P=.24$; and high-risk group $r=-0.02$, $r^2=0.006$, $P=.95$). Correlations between word pair recall after fMR imaging and novel encoding mean fit coefficients also revealed a positive association unique to the low-risk group in the left MTL ROI (low-risk group $r=0.90$, $r^2=0.81$, $P<.001$; and high-risk group $r=0.21$, $r^2=0.045$, $P=.56$) (Figure 3B). Unlike the CVLT scores, however, mean fit coefficients for encoding of repeated word pairs had a positive correlation with recall of repeated word pairs after fMR imaging in the low-risk group ($r=0.90$, $r^2=0.81$, $P<.001$) but not in the high-risk group ($r=0.23$, $r^2=0.06$, $P=.50$).

### Control Analysis

Analysis of the response of voxels within the primary visual cortex revealed strong positive bilateral activations during encoding of novel word pairs compared with a fixation baseline for the high-risk group and the low-risk group. There were no significant clusters of group differences observed within this search region.

### Comment

In this study, we found differences in fMR imaging BOLD signal in many brain areas in nondemented middle-aged adults based on the combined risks of APOE status and family history of dementia. In particular, we found significantly increased BOLD signal in the left MTL associated with novel encoding among individuals at higher risk for AD. In the low-risk group, performances on verbal list learning (ie, the CVLT) and cued recall after fMR imaging were correlated with increased BOLD activation during novel encoding in the left MTL. We confirmed that activations were equivalent between groups in the primary visual cortex, a control area in which no differences were expected. Hence, it appears that between-group differences could not be accounted for by differences in broad underlying physiological factors, age, sex, educational achievement, performance on cued recall of the imaging task, or cognitive function in general. Rather, these fMR imaging findings would appear to be more directly affected by APOE genotype and family history.

Our study replicates previous fMR imaging results among older adult populations, yet it does so among younger, well-matched cognitively normal middle-aged adults. To date, functional neuroimaging changes among younger sample populations of risk groups for AD have been documented primarily using positron emission tomography. In addition to APOE status, we used family history of dementia to load on risk factors in an effort to improve sensitivity of BOLD signal detection and group discrimination, similar to the study by Smith et al, in which increased parietal BOLD activity was demonstrated in a group of middle-aged women during a verbal fluency task. Two fMR imaging studies have previously shown increased BOLD signal in the MTLs of cognitively normal individuals at high risk for AD than in comparable control groups. Bookheimer et al first showed this effect during verbal associative learning or recall in normal aging. To our knowledge, these findings have not been replicated using the same paradigm until the present study. In addition, in the study by Bookheimer et al the finding of increased MTL BOLD signal in the APOE ε4 group may have been affected by the lower delayed recall memory scores in that group. The subjects in that study also had a wide age range, with up to a 16-year age difference among subjects, which may have produced additional variability. Hemodynamic responses can change in an age-related manner, and baseline perfusion and atrophy can change with age, di-

<table>
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<tr>
<th>Brain Region*</th>
<th>Volume, mm³</th>
<th>$r^2$ for High vs Low Risk</th>
<th>Direction of Within-Group Activations†</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk &gt; Low Risk (Hot Colors)</td>
<td>Low Risk</td>
<td>High Risk</td>
<td></td>
</tr>
<tr>
<td>R fusiform and lingual gyrus (18.9R, 73.1P, 7.7I)</td>
<td>7936</td>
<td>0.61</td>
<td>Novel &gt; fixation</td>
</tr>
<tr>
<td>L P cingulate gyrus (7.2L, 46.6P, 23.1S)</td>
<td>6336</td>
<td>0.62</td>
<td>Novel &gt; fixation</td>
</tr>
<tr>
<td>R A middle temporal gyrus (53.4R, 11.1P, 117.8I)</td>
<td>4992</td>
<td>0.64</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>L A middle temporal gyrus (54.9L, 1.0P, 18.4I)</td>
<td>3008</td>
<td>0.60</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>B lingual gyrus (20.5L, 87.3P, 2.4I)</td>
<td>3008</td>
<td>0.60</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>R I frontal gyrus (46.7R, 10.6A, 19.2S)</td>
<td>2944</td>
<td>0.61</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>L parahippocampal gyrus (27.7L, 35.1P, 11.0I)</td>
<td>1920</td>
<td>0.61</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>R P cingulate and cuneus (5.6R, 68.8P, 18.4S)</td>
<td>1664</td>
<td>0.60</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>L P corpus callosum area (9.3L, 22.2P, 28.1S)</td>
<td>1600</td>
<td>0.62</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>R middle temporal gyrus (51.5R, 41.3P, 1.7I)</td>
<td>1536</td>
<td>0.62</td>
<td>Fixation &gt; novel</td>
</tr>
<tr>
<td>R P middle temporal gyrus (39.9R, 69.9P, 22.2S)</td>
<td>1408</td>
<td>0.62</td>
<td>Fixation &gt; novel</td>
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</tbody>
</table>

<table>
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<tr>
<th>Low Risk &gt; High Risk (Cold Colors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L cerebellar hemisphere (28.4L, 86.1P, 20I)</td>
</tr>
<tr>
<td>R I parietal lobe (47.7R, 50.4P, 39.4S)</td>
</tr>
</tbody>
</table>

Abbreviations: A, anterior; B, bilateral; I, inferior; L, left; P, posterior; R, right; S, superior.

*Talairach and Tournoux17 coordinates are given in parentheses.

†All comparisons were significant at the $P = .05$ level. Novel > fixation indicates a relative increase in within-group BOLD signal for this contrast.

Fixation > novel indicates a relative decrease in within-group BOLD signal for this contrast.
rectly affecting BOLD signal response. To address these issues, we selected 2 groups of subjects that were well matched on all demographic variables, narrowing the age ranges (Table 1). Our study groups also showed no significant differences on any cognitive measure. A previous study that used a picture-encoding task found encoding-based BOLD differences by APOE genotype among cognitively normal individuals in their eighth decade of life. The present study replicates these BOLD differences among individuals about 15 years younger, more than a decade earlier than the typical age at onset of AD, and extends the prior findings using a different encoding task.

Findings in our correlational analysis lend support to the notion that between-group BOLD differences in the left MTL are task related and suggest that the 2 risk groups are approaching episodic memory functions in distinct ways. The CVLT and cue recall scores of novel word pairs after fMR imaging demonstrated strong correlations with BOLD signal in the left MTL ROI in the low-risk group but not in the high-risk group. Previous authors have noted a positive correlation between CVLT scores and novel verbal learning in the left MTL of healthy adults. Because the CVLT is a novel verbal encoding task, it is not surprising that the scores did not correlate with activations during repeated word pair presentation, whereas recall scores of the repeated word pairs after fMR imaging did correlate with activations during presentation of repeated word pairs. Furthermore, the differing directions of association between MTL brain response and CVLT or recall performance after fMR imaging in the 2 risk groups are qualitatively similar to previous findings,4 again suggesting that at-risk individuals may be invoking MTL activation of brain resources in distinct ways in an attempt to facilitate performance while learning new information. If such consistencies continue to be observed across studies, collectively they may help determine whether increased activation or decreased activation in a given region represents a compensatory response.

There are limitations of the techniques used in this study. Spatial distortion of echo-planar imaging and the differences in spatial resolution between functional and anatomical images make registration among these images problematic. We used group-averaged anatomical underlays to localize functional signal in an attempt to minimize variation in individual registration to the standardized atlas. Furthermore, our ROI analysis was based on registration of functional data onto a standardized anatomical atlas, not individual anatomies, and needs to be interpreted accordingly. Our analyses did not include segmentation or volumetric between-group comparisons. The BOLD signal can be associated with atrophy, and hippocampal atrophy has been noted to vary by APOE status among subjects with AD and non-demented older populations. However, given the younger ages of our sample and the narrow age ranges of our 2 groups, significant differences in anatomy and cerebral atrophy are unlikely.

Previous positron emission tomography studies have shown differences in resting glucose metabolism specific to the areas of interest in our study population. Furthermore, global baseline perfusion differences can result in between-group differences when contrasting experimental vs baseline conditions. Although our groups did not demonstrate broad physiological differences in our control region (Brodmann area 17), this does not eliminate the possibility that underlying baseline group differences in metabolism or perfusion affected the findings in the novel vs fixation contrast. Last, this study reported cross-sectional comparisons. No follow-up cognitive data have been obtained yet on this group of individuals. Therefore, any discussion of our findings representing a “compensation” for impending dementia, or underlying neuropathologic conditions, is speculative. Longitudinal follow-up is essential to directly test for associations between the present BOLD signal differences and evidence of cognitive decline.

In summary, our study provides further evidence that fMR imaging is a reliable tool for differentiating groups...
at risk for AD. Additional work with larger sample sizes, high field-strength MR imaging, and improved measures of underlying brain physiology among different age ranges is needed to better understand how fMRI imaging findings may be used as a potential biomarker for preclinical AD and in clinical trials. As more information becomes known about AD risk factors, it is increasingly important to focus on detection of preclinical disease, when the use of neuroprotective agents and other disease-altering treatments would be most effective.

Accepted for Publication: May 23, 2005.

Correspondence: Adam S. Fleisher, MD, Department of Neurosciences, University of California, San Diego, 8950 Villa La Jolla Dr, Suite C227, La Jolla, CA 92037 (afleisher@ucsd.edu).

Author Contributions: Study concept and design: Fleisher, Eyler, Thal, and Bondi. Acquisition of data: Fleisher, Houston, Frye, and Jenkins. Analysis and interpretation of data: Fleisher, Houston, Eyler, Thal, and Bondi. Drafting of the manuscript: Fleisher, Houston, Jenkins, and Bondi. Critical revision of the manuscript for important intellectual content: Fleisher, Houston, Eyler, Frye, and Bondi. Statistical analysis: Houston, Eyler, and Bondi. Obtained funding: Fleisher and Bondi. Administrative, technical, and material support: Fleisher, Frye, Jenkins, Thal, and Bondi.

Study supervision: Fleisher, Thal, and Bondi.

Funding/Support: This work was supported by pilot grants NIA P50 AG05131 and NIA RO1 AG12674 from the University of California, San Diego, Alzheimer’s Disease Research Center, and by funds from a Research Enhancement Award Program of the Department of Veterans Affairs Medical Research Service, Washington, DC.

Acknowledgment: We gratefully acknowledge the assistance of the staff, patients, and volunteers of the University of California, San Diego, Alzheimer’s Disease Research Center; Gregory G. Brown, PhD; and the staff of the University of California, San Diego, Laboratory of Cognitive Imaging.

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