MRI-Guided SPECT Perfusion Measures and Volumetric MRI in Prodromal Alzheimer Disease

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Objective: To identify group differences in the prodromal phase of Alzheimer disease (AD) using quantitative single-photon emission computed tomography (SPECT) perfusion and magnetic resonance imaging (MRI) volume measures within specific volumes of interest.

Setting: Gerontology research unit.

Participants: There were 17 healthy controls, 56 non-demented patients with memory problems who did not develop AD during 3 to 5 years of follow-up (questionables), and 27 nondemented patients with memory problems who developed AD during follow-up (converters).

Methods: A Tc 99m hexamethylpropyleneamine oxime SPECT study and an MRI were performed in each participant at baseline. Mean SPECT activity concentration and MRI volume were estimated within 9 structures: rostral anterior cingulate, caudal anterior cingulate, posterior cingulate, hippocampus, entorhinal cortex, basal forebrain, temporal horn, amygdala, and the banks of the superior temporal sulcus. Data were analyzed using overall and pairwise discriminant analysis, and performance in pairwise group discrimination was measured using correlated receiver operating characteristic curve analysis.

Results: The overall (3-group) discriminant function was significant for SPECT (F test, \( P < 0.001 \)) and MRI (F test, \( P < 0.0001 \)). For the SPECT analysis, the ranking of structures for discriminating among the 3 groups was, in order of decreasing discriminating power, caudal anterior cingulate, temporal horn, superior temporal sulcus, entorhinal cortex, hippocampus, rostral anterior cingulate, amygdala, basal forebrain, and posterior cingulate. For the MRI analysis, this ranking was entorhinal cortex, superior temporal sulcus, temporal horn, hippocampus, amygdala, caudal anterior cingulate, rostral anterior cingulate, basal forebrain, and posterior cingulate. Combining the 2 modalities yielded significantly better discrimination performance than did either alone. Furthermore, the correlation between SPECT and MRI measures was low.

Conclusion: Measures of structure activity concentration and volume carry independent information; both reveal group differences in prodromal AD.

Arch Neurol. 2003;60:1066-1072

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and the hippocampus are the most commonly reported findings.8-13

In the present study, we compared MRI volume estimates with SPECT estimates of activity concentration in MRI-guided VOI. The goals were to determine the accuracy of each modality alone in identifying group differences in the prodromal phase of AD and to determine whether the combination of these modalities is significantly better than either one taken separately.

METHODS

PARTICIPANTS

One hundred individuals participated in the study after providing informed consent according to institutional guidelines. These individuals were participants in a large longitudinal study of prodromal AD.14,15 To be included in the study, participants had to be 65 years of age or older and free of significant underlying medical, neurologic, or psychiatric illness based on standard laboratory test results and clinical evaluation findings. Furthermore, they had to be normal or questionable by the Clinical Dementia Rating (CDR) criterion,16 which stages individuals according to their functional ability, with 0 representing normal function and 5 representing the terminal phase of dementia. No one was excluded on the basis of sex or racial or ethnic identity.

At baseline, 17 participants had normal cognition (CDR, 0.0) and 83 met the criteria for “questionable AD” (CDR, 0.5). The mean ± SD age of the 2 groups were nearly equal (73.8 ± 4.8 and 72.9 ± 6.1 years), as were the mean ± SD Mini-Mental State Examination scores17 (29.4 ± 0.9 and 29.1 ± 1.3). After enrollment in the study, participants were evaluated annually. After 3 to 5 years of follow-up, participants were divided into 3 groups—controls, questionables, and converters—based on their functional status at baseline and at follow-up. (Additional details are available in the study by Albert et al.14)

Controls

This group consisted of 17 individuals (mean ± SD age, 73.8 ± 4.8 years) who entered the study with normal cognition (CDR, 0.0; mean ± SD Mini-Mental State Examination score, 29.4 ± 0.9) and who remained cognitively intact after 3 to 5 years of annual follow-up evaluations (CDR, 0.0; mean Mini-Mental State Examination score, 29.3).

Questionables

This group consisted of 56 individuals (mean ± SD age, 72.5 ± 6.9 years). At baseline, these individuals were not demented but had evidence of memory impairment in daily life (CDR, 0.5; mean sum of boxes, 1.01). After 3 to 5 years of follow-up, these individuals remained nondemented but continued to have cognitive impairments (CDR, 0.5; mean sum of boxes, 1.51).

Converters

This group consisted of 27 individuals (mean ± SD age, 73.7 ± 4.1 years). At baseline, these individuals were nondemented but had evidence of mild memory impairment (CDR, 0.5; mean sum of boxes, 1.36). After 3 to 5 years of follow-up, their cognitive difficulties had progressed to the point where they met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria for probable AD (CDR, 1.1; mean sum of boxes, 5.25).18

The annual medical, neurologic, psychiatric, and laboratory evaluations were augmented, as needed, to exclude other potential causes of cognitive decline to establish the diagnosis of probable AD. The SPECT data were not provided to the clinicians making the diagnosis. Four participants died, and a diagnosis of definite AD was confirmed by autopsy examination.19

IMAGING PROCEDURES

At baseline, all study participants underwent SPECT and MRI. Although the imaging data were obtained at baseline, the data were analyzed using the participant’s status on follow-up.

MRI Acquisitions and Procedures

Each participant underwent T1-weighted gradient echo MRI (1.5T Signa; General Electric Medical Systems, Milwaukee, Wis) of the brain (repetition time, 35 milliseconds; echo time, 5 milliseconds; field of view, 220; flip angle, 45°; slice thickness, 1.5 mm; and matrix size, 256 × 256). Nine VOI were outlined manually by skilled operators using methods that have been shown to have high reliability.11,20 Most VOI were selected on the basis of neuropathologic or functional neuroimaging data indicating that they are altered early in the course of AD. However, some of the VOI were selected on the basis of probable involvement in the later stages of disease. Each VOI consisted of a left and right pair of structures.

The brain structures considered in these analyses included the entorhinal cortex (ento), the basal forebrain (basfb), the hippocampus (hipp), the amygdala (amy), the temporal horn (thorn), the banks of the superior temporal sulcus (sts), and 3 sections of the cingulate gyrus: the rostral portion of the anterior cingulate (acing), the caudal portion of the anterior cingulate (mcng), and the posterior cingulate (pcing). Each VOI volume estimate was adjusted for total brain volume, as described in the “Statistical Analysis” subsection. The locations of the MRI VOI are shown in Figure 1.

SPECT Acquisitions and Procedures

Brain SPECT was performed using a dedicated brain gamma camera (CeraSPECT; Digital Scintigraphics Inc, Waltham, Mass) with stationary annular thallium-activated sodium iodide crystal, within which rotates a collimator consisting of 3 parallel-hole segments. Intrinsic spatial resolution is 3.6-mm full width at half maximum, and the system spatial resolution is 8.2-mm full width at half maximum at the center of the field of view21 for technetium (99mTc) (140 keV). Planar views (projections) were acquired 20 minutes after injection of a mean ± SD of 740.0 ± 37.0 MBq (20.0 ± 1.0 mCi) of 99mTc hexamethylpropyleneamine oxime (Ceretec; Amersham, Buckinghamshire, England) with the participants supine, at rest, with eyes open in a darkened room with ambient noise. One hundred twenty projections (128 × 64) were acquired in 30 minutes (isotropic pixel dimension, 1.67 mm) in 13 energy windows encompassing the 80- to 154-keV energy range.

The same 9 VOI were evaluated for SPECT as for MRI. Activity estimation in the SPECT VOI was performed after correcting for scatter, nonuniform attenuation, and variable collimator response using a quantitation strategy based on recent work that has been validated by Monte Carlo simulations22 and by phantom studies.23 First, acquired projections were corrected for scatter using a general spectral method24 by which scatter-corrected projections are formed by linear combination of the pixel counts in each energy window. In a previous study,24 the weighting scheme for data within seventeen 4-keV energy windows, ranging from 92 to 160 keV, was optimized on the basis of the accuracy and precision with which lesion and background activity could be simultaneously estimated. Because the data in the present study were collected in different
energy windows, weights for these windows were determined from the original weights by using spline interpolation.\textsuperscript{23}

After correction for scatter, the projections were reconstructed by the maximum likelihood expectation maximization approach\textsuperscript{25} using an accelerated algorithm based on use of ordered subsets (OSEM)\textsuperscript{26} to yield the perfusion image.

We compensated for the variable collimator response by modeling the distance-dependent component of spatial resolution in the iterative OSEM algorithm.\textsuperscript{26} Attenuation correction was also performed directly in the reconstruction algorithm by modeling the nonuniform attenuation distribution in the OSEM algorithm.\textsuperscript{23} The attenuation map was estimated individually for each participant by using the following procedure. First, projections were reconstructed using OSEM (6 subsets and 8 iterations) without corrections for attenuation and collimator response. This preliminary SPECT image was registered to the MRI using a brain surface–based rigid body transformation.\textsuperscript{27,28} The MRI volume was segmented into bone and soft tissue compartments to yield an attenuation map that was used to correct for nonuniform attenuation as previously described.\textsuperscript{23} Finally, a second OSEM reconstruction (6 subsets) was performed, with corrections for attenuation and variable collimator response incorporated into the iterative algorithm; reconstructed volumes corresponding to 9, 11, 13, 15, 17, and 19 iterations were saved. Mean regional perfusion was calculated from the 3-dimensional volume within the structure boundaries defined on the registered MRI. Figure 2 illustrates the steps involved in the correction and quantitation of the MRI-guided SPECT measures.

\section*{STATISTICAL ANALYSIS}

\subsection*{Overall Linear Discriminant Analysis}

An overall discriminant analysis\textsuperscript{39} was performed to determine whether the 9 VOI values together significantly differentiated the 3 groups (controls, questionables, and converters). For the SPECT analysis, 10 variables were used: the 9 struc-

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{The locations of the 9 volumes of interest used for the magnetic resonance imaging and magnetic resonance imaging–guided single-photon emission computed tomography data: rostral anterior cingulate (blue), caudal anterior cingulate (green), and posterior cingulate (red) (A); temporal horn (purple), hippocampus (blue), and entorhinal cortex (orange) (B); basal forebrain (blue) and amygdala (yellow) (C); and the banks of the superior temporal sulcus (green) (D).}
\end{figure}
tecture activity concentration estimates and the total brain SPECT activity, included to adjust for any possible differences between the groups based on this variable. The covariate method of adjustment for total brain SPECT activity was used in these analyses because it allows a correction to occur only when there is significant correlation between total perfusion and the activity concentration in a particular brain structure. An analogous overall discriminant analysis was performed for the MRI data; the 10 variables included the 9 volume estimates and a measure of intracranial volume. The significance of each discriminant function was tested using an F approximation to Wilks’ λ. The statistical power of the overall analysis is based on the overall sample size, that is, 100 patients, rather than on the sizes of the individual groups.

**Pairwise Discriminant Analysis**

Stepwise discriminant analyses were performed to identify the structures that were most effective in discriminating between the pairs of groups: controls vs converters, controls vs questionables, and questionables vs converters. For each binary analysis, the most discriminating variable was selected by comparing values of Wilks’ λ for the 9 structures of interest (excluding total activity or volume). The next variable was selected by maximizing the partial F statistic for adding a second variable to the first. This procedure was repeated, maximizing the partial F statistic for adding another variable to the set already chosen, until all 9 structures had been ranked. This ranking procedure was performed for 3 sets of variables: (1) the 9 SPECT structure activity estimates, (2) the 9 MRI structure volume estimates, and (3) the combination of SPECT and MRI measures (the ranking procedure was terminated after 9 of the 18 variables had been chosen). The stepwise discriminant analyses were repeated on 2 subgroups of patients obtained by dividing each patient group into 2 to assess the robustness of the rankings (n=49 and 51).

For each pairwise analysis, discriminant scores were calculated for each participant based on the discriminant function for all 9 variables. Next, a correlated receiver operating characteristic (ROC) curve was fitted to the discriminant score data for each analysis. The ROC curve is a plot of true-positive rate (sensitivity) vs false-positive rate (1−specificity) as the decision threshold is varied. Performance in the binary discrimination task is specified by the area under the ROC curve (Az); the most discriminating variable was selected by comparing the ROC curve for the 9 structures of interest (excluding total activity or volume). The next variable was selected by maximizing the partial F statistic for adding another variable to the set already chosen, until all 9 structures had been ranked. This ranking procedure was performed for 3 sets of variables: (1) the 9 SPECT structure activity estimates, (2) the 9 MRI structure volume estimates, and (3) the combination of SPECT and MRI measures (the ranking procedure was terminated after 9 of the 18 variables had been chosen). The stepwise discriminant analyses were repeated on 2 subgroups of patients obtained by dividing each patient group into 2 to assess the robustness of the rankings (n=49 and 51).

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**RESULTS**

**OVERALL LINEAR DISCRIMINANT ANALYSIS**

The overall discriminant function was significant for SPECT (F test, P<.001) and MRI (F test, P<.0001). The most significant overall discriminant function among the 3 groups of patients was obtained for 13 iterations; therefore, the SPECT activity estimates from images reconstructed by 13 iterations of OSEM were used for the remaining analyses. For the SPECT data, the ranking of structures for discriminating among the 3 groups was, in order of decreasing discriminating power, mcing, thorn, sts, ento, hipp, and acing. For the MRI analysis, this ranking was ento, sts, thorn, hipp, amy, and mcing.

**PAIRWISE DISCRIMINANT ANALYSES**

**Controls vs Converters**

Analysis of the SPECT data revealed that the structure with the most power to discriminate controls and converters was mcing. The structure that, combined with mcing, had the next most discriminating power was pcing (it is possible that 2 other structures together have more discriminating power than do mcing and pcing combined; this is also true of later-ranking results). The 6 structures with the most discriminating power were mcing, pcing, sts, basfb, aming, and amy. For the MRI analysis, this ranking was ento, thorn, amy, basfb, sts, and acing. When the SPECT and MRI measures were combined, the best structures discriminating between controls and converters (of 18 structures) included MRI and SPECT variables: ento_MRI, mcing_SPECT, mcing_MRI, thorn_MRI, acing_MRI, and sts_SPECT. Similar ranking results were obtained using the subgroups of patients.

**Controls vs Questionables**

The ranking of the best SPECT variables was, in order of decreasing discriminating power, thorn, mcing, basfb, hipp, pcing, and sts. For the MRI analysis, this ranking was ento, amy, sts, basfb, mcing, and pcing. When the SPECT and MRI measures were combined, the best structures discriminating between controls and questionables were ento_MRI, amy_MRI, sts_MRI, basfb_MRI, thorn_SPECT, and sts_SPECT. The best 6 structures resulting from the pairwise discriminant analyses of the 2 subgroups of patients yielded similar results for the 4 best structures.

**Questionables vs Converters**

The ranking of the 6 best SPECT variables was, in order of decreasing discriminating power, amy, sts, basfb, mcing, hipp, and acing. For the MRI analysis, this ranking was acing, sts, basfb, thorn, amy, and hipp. When the SPECT and MRI variables were combined, the best structures discriminating between questionables and converters were amy_SPECT, acing_MRI, basfb_MRI, basfb_SPECT, pcing_SPECT, and pcing_MRI. These results were consistent with those obtained for each subgroup of patients. Figures 3, 4, and 5 show the ROC curves measuring the performance in discriminating between controls and converters, controls and questionables, and questionables and converters, respectively, when using SPECT, MRI, or combined SPECT and MRI data. For SPECT, the mean±SD Az was 0.962±0.028 for controls vs converters, 0.969±0.019 for controls vs questionables, and 0.879±0.037 for questionables vs converters. For MRI, the comparable mean±SD Az values were 0.990±0.010, 0.986±0.010, and 0.843±0.049, respectively. The mean±SD Az values were significantly higher for combined SPECT and MRI data than for each modality alone: 0.993±0.010 for controls vs converters, 0.987±0.013 for controls vs questionables, and 0.935±0.026 for questionables vs converters (P<.05). The corre-
yielded better performance at the clinically interesting
task of greatest clinical interest, that is, discrimination between questionables and converters (Az=0.843 and 0.879, respectively) in the task of greatest clinical interest, that is, discrimination between questionables and converters (Az=0.843 and 0.879, respectively) in the task of greatest clinical interest, that is, discrimination between questionables and converters.

Most important, combining the best MRI and SPECT measures yielded systematically better results than using either MRI or SPECT data alone, implying that independent information is present in the SPECT and MRI data. This is also seen in the ranking of the structures, which differed for the 2 modalities, and in the ranking obtained when combining the best SPECT and MRI measures as perfusion and volume of certain structures, such as memory, were both selected. Finally, the low correlations (0.0083–0.0229) between data from the 2 modalities further confirm the independent character of the information present in SPECT and MRI. This suggests that the 2 modalities, used in a complementary manner, will yield the best information on prodromal AD.

Even when combining SPECT and MRI information, the performance in discriminating between questionables and converters, the most clinically interesting task, was significantly less (Az=0.93) than that for discrimination between controls and converters (Az=0.99) or controls and questionables (Az=0.98) (P<.01). This is most likely because some of the questionable participants are destined to develop AD at a later time and, therefore, have SPECT perfusion and MRI volume abnormalities that are similar to those of converters. The decline in sum of boxes among the participants who remained questionable on follow-up (from 1.01 to 1.51) supports this hypothesis.

It is unlikely that the discriminating power of the SPECT variables can be attributed to disease-related at-
rophy combined with limited spatial resolution. Our re-
construction methods led to improved spatial resolu-
tion and, consequently, minimal confounding between
SPECT activity concentration estimates and structure vol-
ume. To support this assertion, we estimated the ef-
fects of limited spatial resolution on estimates of activ-
ity concentration within the entorhinal cortex, in which,
because of its small size, atrophy effects would be great-
est. To estimate the magnitude of the underestimation of
entorhinal activity due to this phenomenon, we mod-
eled the entorhinal cortex as a cylinder, with an axial
length twice its diameter. The mean diameter of the en-
torhinal cortex in the present study was 8 mm. The spa-
tial resolution in our images was 6-mm full width at half
maximum. This implies an underestimation of entorhir-
inal activity of 12%, taking into account surrounding brain
structures. This degree of bias is comparable to the best
accuracy (10% error) that can be achieved when com-
penating for all physical factors affecting quantitative
SPECT.31

The specific ranking of the structures is also of in-
terest. For the MRI variables, the most discriminating mea-
sures pertain to the medial temporal lobe (eg, the ento-
rhinal cortex). This is consistent with several previous
studies8,10 and with the fact that a memory deficit is the
initial symptom seen in individuals with prodromal AD.
(Additional details are available in the review by Albert
and Moss.) For the SPECT variables, the most discrimi-
nating measures pertain to the cingulate, particularly
the caudal portion of the anterior cingulate. The middle por-
tion of the cingulate has only recently been identified as
demonstrating altered perfusion in prodromal AD and
has been hypothesized to be related to the deficits in ex-
cutive function demonstrated in this early phase of dis-
ease.3 Differences between the present findings and those
of previous studies are probably related to the large quan-
tity of VOI examined in the present study and to the rank-
ing strategy.

Moreover, the estimates of the A zs are affected by
resubstitution bias, since the binary classification tasks
were accomplished using rules established with the same
participants being classified. Therefore, the ROC curve
performance measures obtained herein may be better than
those achieved in a new group of individuals. They can,
however, be viewed as upper bounds on the ability of the
image-derived measures to discriminate the groups.

In conclusion, quantitative brain SPECT and MRI
identify group differences in the prodromal phase of AD.
The most discriminating brain regions identified by SPECT
are task dependent and differ from those identified by MRI. Combining information from SPECT and MRI yields the best discrimination performance.

Accepted for publication March 11, 2003.

Author contributions: Study concept and design (Drs El Fakhri, Kijewski, Johnson, and Albert); acquisition of data (Drs Johnson and Killiany and Mr Zimmerman); analysis and interpretation of data (Drs El Fakhri, Kijewski, and Albert); drafting of the manuscript (Drs El Fakhri, Kijewski, and Albert); critical revision of the manuscript for important intellectual content (Drs El Fakhri, Kijewski, Johnson, and Albert and Mr Zimmerman); statisti-
cal expertise (Drs El Fakhri and Kijewski); obtained funding (Drs Kijewski, Johnson, and Albert); administrative, technical, and material support (Dr El Fakhri and Messrs Syrkin, Becker, and Zimmerman); study supervision (Drs El Fakhri and Kijewski).

This work was supported in part by grants RO1-EB000802, PO1-AG04953, and RO1-CA78936 from the National Institutes of Health, Bethesda, Md.

We thank Mary Hyde, PhD, for data management and Kenneth Jones, EdD, for assistance with statistical analy-

sis. The manuscript benefited greatly from the suggestions of 2 anonymous reviewers.

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criteria for the Neuropsychological Assessment of Alzheimer’s Disease. Consensus

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Error in Figure Key. In the original contribution titled “Dietary Fats and the Risk of Incident Alzheimer Disease,” published in the February 2003 issue of the ARCHIVES (2003;60:194-200), the key to Figure 2 was reversed during processing for production. Figure 2 is reprinted correctly here.

Figure 2. The 1-year risk of incident Alzheimer disease (AD) by quintile median levels of trans-unsaturated fat and polyunsaturated fat. Data are based on a multivariable logistic model adjusted for age (years), sex, race, education (years), APOE e4, time period of observation, trans-unsaturated fat (continuous log transformed), polyunsaturated fat (continuous log transformed), and the interactive term for trans and polyunsaturated fats (P=.04).