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, $P < .001$) and MRI (F test, $P < .0001$). 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.

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SINGLE-PHOTON EMISSION computed tomography (SPECT) reveals perfusion abnormalities in patients with established Alzheimer disease (AD). The most consistent finding reported in these studies is decreased perfusion in the temporoparietal association neocortex in mildly and moderately impaired patients with probable AD compared with healthy controls. More recently, several research groups have attempted to identify brain perfusion patterns that predict subsequent development of AD. These efforts have practical, as well as theoretical, significance, because early prediction of AD would make it possible to implement strategies to prevent or delay dementia. Johnson et al used principal component analysis to identify decreased perfusion in the hippocampal-amygdaloid complex and in the anterior and posterior cingulate in prodromal AD. This approach does not require a priori assumptions about the locations of discriminating regions, but it may not yield insight into the role of particular brain structures in the development of AD. Other SPECT studies targeted specific volumes of interest (VOI) and reported that perfusion in the posterior cingulate declines in prodromal AD. None of these studies targeted all of the small brain regions believed to be involved in prodromal AD. Several magnetic resonance imaging (MRI) studies have, similarly, sought to determine whether decreased volume in certain brain structures characterizes prodromal AD. Significant volume changes in the entorhinal cortex...
and the hippocampus are the most commonly reported findings.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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, 0.3). 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 scores\textsuperscript{17} (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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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\textdegree; 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.\textsuperscript{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 (basf), the hippocampus (hipp), the amygdala (amy), the temporal horn (thorn), the banks of the superior temporal sulcus (st), and 3 sections of the cingulate gyrus: the rostral portion of the anterior cingulate (acing), the caudal portion of the anterior cingulate (mcing), 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. Intrinsically 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 view\textsuperscript{21} for technetium (\textsuperscript{99m}Tc) (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 \textsuperscript{99m}Tc hexamethylpropyleneimine 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 simulations\textsuperscript{22} and by phantom studies.\textsuperscript{23} First, acquired projections were corrected for scatter using a general spectral method\textsuperscript{24} by which scatter-corrected projections are formed by linear combination of the pixel counts in each energy window. In a previous study,\textsuperscript{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.

**STATISTICAL ANALYSIS**

**Overall Linear Discriminant Analysis**

An overall discriminant analysis\textsuperscript{29} 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-
ture 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’ lambda (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’ lambda (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); an Az of 1.0 corresponds to perfect performance, and an Az of 0.5 implies chance performance. Correlated ROC curves were computed for the SPECT and the MRI measures and for the MRI and the combined SPECT and MRI performance. The ROC curve-fitting procedure provided estimates of correlation between the MRI and the SPECT data and between the MRI and the combined SPECT and MRI data.

RESULTS

OVERALL LINEAR DISCRIMINANT ANALYSIS

The overall discriminant function was significant for SPECT (F test, P<.001) and MRI (F test, P<.001). 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, thorn, amy, basfb, sts, and acing. When the SPECT and MRI measures were combined, the best structures discriminating between controls and converters were mcing_MRI, thorn_MRI, acing_MRI, and sts_SPECT. Similar ranking results were obtained using the subgroups of patients.

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 pcng combined; this is also true of later-ranking results). The 6 structures with the most discriminating power were mcing, pcng, sts, 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, pcng, and sts. For the MRI analysis, this ranking was ento, amy, sts, basfb, mcing, and pcng. 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 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, pcng_SPECT, and pcng_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: 0.995±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 cor-
The SPECT and MRI variables obtained at baseline are highly significant predictors of the future development of AD. Although MRI and SPECT measures yielded similar discrimination accuracy (Az = 0.843 and 0.879, respectively) in the task of greatest clinical interest, that is, discrimination between questionables and converters, close examination of these curves shows that MRI yielded better performance at the clinically interesting low false-positive rate of less than 10% (high specificity regime), whereas SPECT outperformed MRI at false-positive rates greater than 10%. The MRI measures yielded greater discrimination for controls vs converters and controls vs questionables than did the SPECT measures. The higher performance obtained in this work compared with previous studies11 resulted from the larger number of brain structures considered (9 instead of 3) and the inclusion of structures that contribute significantly to the discrimination, for example, the basal forebrain, the hippocampus, the temporal horn, the amygdala, and the banks of the superior temporal sulcus.

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 mcing, 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 reconstruction methods led to improved spatial resolution and, consequently, minimal confounding between SPECT activity concentration estimates and structure volume. To support this assertion, we estimated the effects of limited spatial resolution on estimates of activity concentration within the entorhinal cortex, in which, because of its small size, atrophy effects would be greatest. To estimate the magnitude of the underestimation of entorhinal activity due to this phenomenon, we modeled the entorhinal cortex as a cylinder, with an axial length twice its diameter. The mean diameter of the entorhinal cortex in the present study was 8 mm. The spatial resolution in our images was 6-mm full width at half maximum. This implies an underestimation of entorhinal 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 compensating for all physical factors affecting quantitative SPECT.

The specific ranking of the structures is also of interest. For the MRI variables, the most discriminating measures pertain to the medial temporal lobe (eg, the entorhinal cortex). This is consistent with several previous studies\(^8,10\) 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.\(^23\)) For the SPECT variables, the most discriminating measures pertain to the cingulate, particularly the caudal portion of the anterior cingulate. The middle portion 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 executive function demonstrated in this early phase of disease.\(^7\) Differences between the present findings and those of previous studies are probably related to the large quantity of VOI examined in the present study and to the ranking strategy.

Moreover, the estimates of the A, 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.

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Correction

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](image-url)

**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 ε4, 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).