# $^{99m}$Tc Hexamethyl-Propylene-Aminoxime Single-Photon Emission Computed Tomography Prediction of Conversion From Mild Cognitive Impairment to Alzheimer Disease

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**Objective:** *To examine the utility of single-photon emission computed tomography (SPECT) to predict conversion from mild cognitive impairment (MCI) to Alzheimer disease (AD).* **Design:** *Longitudinal, prospective study.* **Setting:** *University-based memory disorders clinic.* **Participants:** *One hundred twenty seven patients with MCI and 59 healthy comparison subjects followed up for 1–9 years.* **Measurements:** *Diagnostic evaluation, neuropsychological tests, social/cognitive function, olfactory identification, apolipoprotein E genotype, magnetic resonance imaging, and brain $^{99m}$Tc hexamethyl-propylene-aminoxime SPECT scan with visual ratings, and region of interest (ROI) analyses were done.* **Results:** *Visual ratings of SPECT temporal and parietal blood flow did not distinguish eventual MCI converters to AD (N = 31) from nonconverters (N = 96), but the global rating predicted conversion (41.9% sensitivity and 82.3% specificity, Fisher's exact test p = 0.013). Blood flow in each ROI was not predictive, but when dichotomized at the median value of the patients with MCI, low flow increased the hazard of conversion to AD for parietal (hazard ratio: 2.96, 95% confidence interval: 1.16–7.53, p = 0.023) and medial temporal regions (hazard ratio: 3.12, 95% confidence interval: 1.14–8.56, p = 0.027). In the 3-year follow-up sample, low parietal (p <0.05) and medial temporal (p <0.01) flow predicted conversion to AD, with or without controlling for age, Mini-Mental State Examina-*

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*tion, and apolipoprotein E ϵ4 genotype. These measures lost significance when other strong predictors were included in logistic regression analyses: verbal memory, social/cognitive functioning, olfactory identification deficits, hippocampal, and entorhinal cortex volumes.* **Conclusions:** *SPECT visual ratings showed limited utility in predicting MCI conversion to AD. The modest predictive utility of quantified low parietal and medial temporal flow using SPECT may decrease when other stronger predictors are available.* (Am J Geriatr Psychiatry 2010; 18:959–972)

**Key Words:** Mild cognitive impairment, Alzheimer disease, prediction, SPECT, clinical utility

Alzheimer disease (AD) accounts for 60%–70% of cases of dementia and more than 13 million cases are expected in the United States by 2050.[1] Mild cognitive impairment (MCI) is defined by subjective memory complaints and objective cognitive impairment, primarily memory deficits, without significant functional impairment.[2] MCI often transitions to Alzheimer disease (AD). In clinical samples, the annual conversion rate from MCI to AD is 8%–15%,[3] and most conversions occur within 3 years of presentation.[3]

Hippocampal and entorhinal cortex atrophy on magnetic resonance (MR) imaging (MRI) scan of the brain strongly predict conversion from MCI to AD, but their accuracy is insufficient for use as the sole predictor.[4,5] Functional neuroimaging techniques include single-photon emission computed tomography (SPECT) and positron emission tomography (PET). 18-fluorodeoxyglucose ($^{18}$FDG) PET shows hypometabolism in patients with AD compared with healthy comparison subjects[6,7] but may not be specific to AD.[8] $^{18}$FDG-PET studies in small samples of patients with MCI show that lower temporoparietal and posterior cingulate hypometabolism may characterize future converters to AD.[9,10]

SPECT is less expensive and more widely available. For $^{99m}$Tc hexamethyl-propylene-aminoxime (HMPAO) SPECT, decreased blood flow in parietal, temporal, and posterior cingulate cortex characterizes patients with AD.[10–15] The few studies that evaluated SPECT for predicting MCI conversion to AD, mainly in small samples (Table 1), suggest moderate sensitivity and specificity for region of interest (ROI) and statistical parametric mapping-based analytic methods[13,16] (Table 1). The accuracy of visual SPECT ratings to predict AD in patients with MCI has not been evaluated in longitudinal studies (Table 1), even though SPECT visual diagnostic reads are commonly used for this purpose. In a cross-sectional study of patients with MCI and comparison subjects, Høgh et al.[17] reported an overall accuracy rate of 89% in comparing dichotomous visual versus ROI ratings of SPECT abnormality.

In a single-site, long-term study of cognitively impaired outpatients without dementia at initial evaluation, we reported that specific cognitive deficits, olfactory identification deficits, informant report of functional deficits, and hippocampal and entorhinal cortex atrophy on MRI scan of brain predicted conversion from MCI to AD and combining these predictors led to strong predictive accuracy.[3] In most study participants, $^{99m}$Tc HMPAO SPECT was conducted at baseline evaluation. We evaluated the utility of expert visual ratings and ROI-derived SPECT indices in predicting conversion from MCI to AD and their added utility to other predictors.[3]

## MATERIALS AND METHODS

### Participants

Patients presented with memory complaints to a Memory Disorders Clinic jointly run by Psychiatry and Neurology at New York State Psychiatric Institute/Columbia University and met study criteria for cognitive impairment without dementia and without a specific identifiable cause. All subjects signed informed consent in this Institutional Review Board (IRB)-approved protocol.

**TABLE 1. Prediction of MCI Conversion to AD Using SPECT. For the Study to be Included in the Table, Baseline SPECT in Minimum 20 Patients With MCI Followed Up for Minimum 1 Year Was Required**

| Authors | Year | Sample | SPECT | Visual Ratings | SPM or ROI Analyses | Results | Sensitivity, Specificity, AUC | Comment |
|---|---|---|---|---|---|---|---|---|
| Okamura et al.[31] | 2002 | 17 MCI converters and seven MCI nonconverters (23 AD and five controls) | $^{123}$IMP, 2–3 years follow-up | No | MCI converters versus nonconverters, ROI: posterior cingulate, temporoparietal ratio to cerebellum | CSF tau/CBF index best for posterior cingulate among four such indices, AUC = 0.96 | Sensitivity 88.5% and specificity 90% | No MRI for coregistration or partial volume correction; small sample of MCI converters/ nonconverters |
| Huang et al.[12] | 2002 | 54 MCI and 17 converters | $^{99}$Tc-HMPAO, 1–4 years follow-up | No | 24 cortical regions, cerebellar ratio, normal template coregistration | Left posterior cingulate significant in MCI decliners; AUC 74%–76% | Not provided | No MRI |
| Huang et al.[16] | 2003 | 54 MCI nonconverters and 28 MCI converters (20 controls) | $^{99}$Tc-HMPAO, 1–4 years follow-up | No | SPM, normalized to global and then cerebellar CBF, plus voxel of interest (VOI) analysis | AUC increased from 75% to 77% for left parietal CBF to 82%–84% after including neuropsych tests | Not provided | Decreased parietal, increased prefrontal flow in MCI decliners. No MRI |
| Encinas et al.[32] | 2003 | 42 MCI and 21 converters | $^{99}$Tc-ECD, 1–3 year follow-up | No | Cerebellar normalization | Decreased flow in frontal, parietal, and temporal regions | Sensitivity and specificity of 75%–80% for these regions | No MRI |
| Borroni et al.[33] | 2005 | 33 MCI, 21 converters, and 12 nonconverters | $^{99}$Tc-ECD SPECT, 1.5–4 years follow-up | No | ROI to cerebellum | Platelet amyloid precursor protein and SPECT | 95% sensitivity and 75% specificity | Small sample |
| Hirao et al.[34] | 2005 | 52 MCI converters, and 24 MCI nonconverters (57 controls) | $^{99}$Tc-ECD, 3-year follow-up | No | SPM, MNI template, proportional global scaling to adjust for global flow. Retrospective analysis | Temporoparietal, precuneus and posterior cingulate flow reductions in converters compared to nonconverters | Not provided | No MRI, high proportion of converters compared to other studies |
| Borroni et al.[14] | 2006 | MCI 18 converters and 9 nonconverters | $^{99}$Tc-ECD SPECT, 2-year follow-up | No | SPM, template | Combining SPECT data with several cognitive test scores | Based on PCA, 77.8% sensitivity, and 77.8% specificity | No MRI |
| Huang et al.[35] | 2007 | 16 MCI converters and 23 MCI nonconverters (20 controls) | $^{99}$Tc-HMPAO, 1–2 years follow-up | No | SSM based on 46 VOI map, used Tailarach template | Combined SPECT and neuropsych measures | Diagnostic accuracy 82% and 84%, combined 92% | No MRI |

(*Continued*)

**TABLE 1.** (*Continued*)

| Authors | Year | Sample | SPECT | Visual Ratings | SPM or ROI Analyses | Results | Sensitivity, Specificity, AUC | Comment |
|---|---|---|---|---|---|---|---|---|
| Johnson et al.[13] | 2007 | CDR 0.5 study; 24 converters, 38 stable nonconverters, and 43 decliners nonconverters (34 AD and 19 controls) | $^{99}$Tc-HMPAO, followed up annually for up to 5 years | No | SPM, Voxel-based data normalized to cerebellum | Decreased perfusion in caudal anterior cingulate and posterior cingulate, but increase in rostral anterior cingulate in converters | Posterior cingulate 79% sensitivity and 67% specificity for converters versus nonconverter decliners | No MRI, multiple subgroups closely related to MCI |
| Gabryelewicz et al.[36] | 2007 | 42 stable MCI and 63 declined of whom 23 converted to AD | $^{99}$Tc-HMPAO followed up annually for 3 years | No | Semiquantitative SPECT analysis using four axial slices | SPECT: no differences, CT scan: temporal lobe atrophy indices predicted conversion | Not provided | Nonstandard SPECT analyses |
| Caroli et al.[37] | 2007 | 23 MCI, 9 converters, and 17 controls | $^{99}$Tc-ECD, followed up 1–2 years | No | SPM and VBM, used combined SPECT/MRI template | Parahippocampal and inferior temporal hypoperfusion predicted conversion; retrosplenial hypoperfusion did not | Not provided | Individualized SPECT-MRI coregistration |
| Caffarra et al.[38] | 2008 | 19 Amnestic MCI, 16 exec dysfunc mCI, 25 multidomain MCI, and 15 controls | $^{99}$Tc-HMPAO, mainly cross-sectional, 1-year follow-up in subsample | No | SPM, voxel-based analysis, cerebellum reference | Amnestic MCI: decreased perfusion in frontal and medial temporal regions. Multidomain MCI similar to amnestic MCI and had left posterior cingulate hypoperfusion | Not provided | Minimal prediction analyses summarized as no differences between stable MCI and converters to AD |
| Nobili et al.[39] | 2009 | MCI 12 converters, 19 decliners, and 43 stable | $^{99}$Tc-HMPAO, 2-year follow-up | No | ROI 6 regions | Hippocampal flow reduction best predictor, parietal also significant | Hippocampus 81% sensitivity and 86% specificity | Prediction stronger for AD converters versus nonconverters compared to decliners versus nondecliners |
| Habert et al.[40] | 2009 | MCI 11 converters and 72 nonconverters | $^{99}$Tc-ECD, 3-year follow-up | No | SPM | Right parietal and hippocampal flow reductions in converters | Combining hippocampus and parietal, 82% sensitivity and 90% specificity | Exclusion of outliers strengthened findings. Low conversion rate to AD |

### Eligibility Criteria

*Patients With MCI.* Inclusion criteria were age 41–85 years, cognitive impairment lasting ≥6 months and ≤10 years, and Folstein Mini-Mental State Examination (MMSE) score ≥22/30.[3] Neuropsychological screening inclusion guidelines were Folstein MMSE recall ≤two thirds objects at 5 minutes, Selective Reminding Test (SRT) delayed recall score >1 standard deviation [SD] below norms, or Wechsler Adult Intelligence Scale (WAIS)-R performance intelligence quotient score ≥10 points below WAIS-R verbal intelligence quotient score. /Patients without these deficits were eligible if they met three criteria: subjective complaint of memory decline, informant's confirmation of memory decline, and modified Blessed Functional Activity Scale score ≥1 on the first eight memory-related cognitive and functional items.[18] For all subjects who met the above criteria, final determination for inclusion was based on a consensus diagnosis between two expert raters (DPD and YS) who reviewed clinical, functional and neuropsychological information, laboratory test results, and MRI radiological reads.

This study began before MCI criteria were established.[2] Because all patients had subjective memory complaints and completed an identical neuropsychological test battery, baseline MCI subtype was determined post hoc by using age, education, and sex-based regression norms.[19] Using this approach, 73% of patients met criteria for amnestic MCI with or without other cognitive domain deficits, 13.5% had nonamnestic MCI, and 13.5% had cognitive scores <1.5 SD below norms, i.e., insufficient to meet MCI criteria.[3]

Exclusion criteria were a diagnosis of dementia, schizophrenia, current major affective disorder, alcohol/substance dependence, history of stroke, cortical stroke or infarct ≥2 cm in diameter based on MRI scan, cognitive impairment entirely caused by medications, or other major neurologic illness, e.g., Parkinson disease. Low-dose hypnotics, antidepressants, cholinesterase inhibitors, and memantine (latter two prescribed in <10% of patients) were permitted, with stable dosage required for 30 days pre-SPECT scan.

*Healthy Comparison Subjects.* Healthy comparison subjects were recruited primarily by advertisement, had normative MMSE and SRT test scores, met all other inclusion/exclusion criteria, signed informed consent, and were group matched to patients on age and sex. All patients were followed up at 6-month intervals, and healthy comparison subjects were followed up annually.

### Procedures

History, physical, neurologic, and psychiatric examinations were completed. Laboratory tests included complete blood count (CBC), serum electrolytes, thyroid, liver and renal function tests, rapid plasma reagin, serum vitamin $B_{12}$, and folate levels. MRI scan and SPECT scan of brain were conducted within 3 months of baseline.

All subjects received an annual neuropsychological test battery, reviewed by an experienced neuropsychologist (YS). Two expert raters (DPD and YS) made a consensus diagnosis at each follow-up, while remaining blind to data from prior visits. The diagnosis of dementia was based on *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria and the diagnosis of possible or probable AD on National Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association criteria.[20] The endpoint of conversion to AD required this diagnosis at two consecutive annual assessments.

### Baseline Predictors of Future Conversion to AD

At study inception, predictors were chosen based on the scientific literature. Among five neuropsychological variables, SRT total recall (12-item, 6-trial sum score) and WAIS-R digit symbol were the strongest predictors.[3] Based on apolipoprotein E genotype, subjects were classified as ϵ4 carriers (ϵ3/ϵ4, ϵ2/ϵ4, or ϵ4/4) or ϵ4 noncarriers.[21] The scratch and sniff University of Pennsylvania Smell Identification Test (UPSIT) score (range = 0–40) was based on recognition of 40 microencapsulated common odorants in a multiple-choice format. The informant report on the Pfeffer Functional Activities Questionnaire (range = 0–10) was used to assess 10 cognitive/social functioning activities.[22,23] Predictors from structural MRI scan were hippocampal and entorhinal cortex volume[5] measured by a single rater (GHP) who established high interrater reliability on 10 scans with expert raters: hippocampal volume intraclass correlation coefficient (ICC) = 0.90, parahippocampal gyrus volume ICC = 0.96, and entorhinal cortex volume ICC = 0.92. The rater blindly rerated 10 scans

that she had rated over a year earlier, and showed high intrarater reliability: hippocampal volume ICC = 0.98, parahippocampal gyrus volume ICC = 0.97, and entorhinal cortex volume ICC = 0.99.[5]

### MRI Acquisition

At baseline, all subjects had a brain MRI scan acquired on the same GE 1.5-T Signa 5X unit that included the following sequences: 1) T1-weighted axial images parallel to the temporal horns using a spin echo sequence with repetition time (TR):550, echo time (TE):11, 5-mm slice thickness without gap, matrix: 256 × 192, number of extractions (NEX) = 1, and 24-cm field of view (FOV); 2) three-dimensional coronal volume spoiled gradient recalled echo sequence, perpendicular to the temporal horns, with TR:34, TE:13, flip angle 45°, 2-mm-thick contiguous slices, matrix 256 × 256, NEX = 1, and a rectangular FOV of 24 ×18 cm.

Anatomical boundaries used for drawing the ROIs were as follows:

*Hippocampus.* The anterior boundary was the amygdala with the transition cortex between the amygdala cortical nucleus and hippocampus excluded by making a perpendicular section at the level of the semilunar gyrus. The lateral border of the hippocampus was the medial wall of the temporal horn. Anteriorly, the superior border was defined by the temporal horn and fimbria, the medial border by the ambient cistern, and the inferior border by the uncal sulcus and parahippocampal gyrus. More posteriorly, the hippocampal body's medial boundary was the transverse fissure and its inferior boundary the parahippocampal gyrus (medial part of the subiculum if the uncal sulcus was not visible). Because the interface between the lateral portion of the subiculum and the hippocampus (Ammon horn) cannot be distinguished, this portion was included in the hippocampus and not the parahippocampal gyrus.

*Parahippocampal Gyrus.* The parahippocampal gyrus volume included the medial portion of the subiculum, the entorhinal cortex, the transentorhinal cortex, and the parahippocampal neocortex and white matter. The medial border was the ambient cistern, and the inferior border was the tentorium cerebelli. In anterior sections, the superior border of the parahippocampal gyrus was the hippocampus and the uncal sulcus. In more posterior sections, the superior boundary was the hippocampus laterally and the transverse fissure. The anterior and posterior boundaries of the parahippocampal gyrus corresponded to the same level (slice) as the anterior and posterior boundaries of the hippocampus. This approach standardized the procedures across all subjects but may have led to exclusion of the anterior-most and posterior-most portions of both structures.

*Posterior Cingulate.* In a sagittal section, the posterior commissure was identified. The corresponding coronal slice was the anterior boundary of the posterior cingulate. Using the longitudinal fissure as the medial boundary, the fissure was drawn from the superior portion of the corpus callosum until the cingulate sulcus (first/most inferior sulcus). The sulcus and white matter were cut through to return to the superior boundary of callosal sulcus. This was followed up until 2 mm posterior to the splenium of the corpus callosum aimed at covering the retrosplenial cortex.

*Parietal Lobe.* Anterior boundary was the central sulcus. Inferior boundary was the extended plane of the Sylvian fissure until we reach the parietooccipital fissure. The inferior boundary of the parietal lobe was modified to follow the parietooccipital fissure. Drawing began on the most anterior slice and three slices posterior, making a box according to the set boundaries of the longitudinal fissure, the parietooccipital fissure, and the Sylvian fissure (parietal lobe drawing restricted to this defined region to ensure complete data in all subjects).

*Sensorimotor Cortex (Reference Region).* On axial slices, the central sulcus was identified on both sides. The somatomotor cortex is located on the anterior bank of the central sulcus, in the dorsal part of the precentral gyrus. The precentral gyrus is separated by the central sulcus from the postcentral gyrus. Its anterior border is the precentral sulcus, whereas inferiorly it borders to the lateral fissure (Sylvian fissure). The postcentral gyrus has the primary somatosensori cortex and is the posterior boundary of the central sulcus. Medially, it is contiguous with the paracentral lobule. The pre and postcentral gyri of each side were traced as a single ROI to determine the sensorimotor cortex.

### SPECT Acquisition

Subjects were imaged at rest in a 12-detector head SPECT unit (Strichman Neuro900) equipped with

high-resolution collimator. In-slice and *z*-axis resolution were 5 mm full-width half-maximum. Daily quality control procedures included sensitivity and gain adjustments.

In the SPECT gantry, subjects were restrained with a Vac-Pac headholder. Head alignment was based on the orbito-meatal line and inion-nasion defined midline. After intravenous injection of $^{99m}$Tc-HMPAO (mean MBq = 767.59, SD = 27.24), an initial series of 40 × 20-second positioning scans at orbito-meatal +4 mm level were acquired and quickly reconstructed using slice-by-slice filtered back projection using the multidetector Wiener filter that depends on the point-spread functions of detectors and total counts per slice and no attenuation correction.[24] These images were used to verify brain positioning and orientation. Formal acquisition began at 30-minute postinjection and was reconstructed in 20 contiguous 4 mm intervals to cover the entire brain. Maximum a posteriori reconstruction, including scatter and attenuation correction, was based on NeuroFocus software (NeuroFocus900 version 2.94, Neurophysics Corporation, Shirley, MA). Images were binned into 128 × 128 × 20 matrix. Immediately after the procedure, the syringe used for injection was imaged for residual activity and then placed in a calibrator to verify the injected dose.

### Image Analysis

The SPECT data were analyzed using two methods: visual ratings and quantitative ROI analysis.

*Visual Ratings of Hypoperfusion.* Consensus baseline severity ratings for blood flow reductions (0 = normal, 1 = mild, 2 = moderate, and 3 = severe flow reduction) were made for the medial temporal, lateral temporal, medial parietal, and lateral parietal regions. In the same rating session, taking into account these regional ratings, global consensus ratings were made for AD (absent, questionable, possible, and probable).

An experienced nuclear medicine radiologist (RLVH, Chief of Nuclear Medicine at Columbia University) and an attending psychiatrist experienced in SPECT and PET research (LSK) established interrater reliability in 12 healthy comparison subjects (ICC = 0.86–0.98 for severity ratings) before conducting study ratings. The two raters jointly evaluated all images to obtain consensus ratings in patients with MCI. The raters had baseline demographic information (age and sex) and brief clinical history but remained blind to neuropsychological, MRI scan, and all follow-up clinical data.

### Quantitative Analysis of SPECT Images

Coronal MR images were coregistered with axial MR images using FMRIB Software Library (FSLs) Oxford Centre for Functional MRI of the Brain (FMRIB) Linear Image Registration Tool and rigid body transform model. Independently, SPECT images were coregistered to axial MR images using FMRIB Linear Image Registration Tool. The inverse transformation was computed and used to coregister SPECT images with high-resolution coronal MR image. Next, the coronal MR images were segmented into CSF, gray matter, and white matter using statistical parametric mapping-5. The resulting tissue masks were used to correct the SPECT images for partial volume effect based on segmentation of high-resolution anatomic MR images into CSF, gray matter, and white matter.[25] Proper alignment between images or segmentations was checked at each stage by comparing five slices from each image for every subject. The ROIs were overlaid onto the corrected SPECT image and the average value extracted within each ROI (excluding non positive values and areas outside the gray matter) using Matlab.

ROIs for the hippocampus, parahippocampal gyrus, posterior cingulate, and parietal regions were drawn on the coronal MR image and overlaid onto the corrected SPECT image, and the average value computed using a locally developed MATLAB program. Nonpositive values and areas outside the gray matter were excluded.

All ROI values represent the ratio of the specific ROI to sensorimotor cortex that has the advantages of being large, located on the cortical surface, and being relatively well preserved in AD and other dementias. In SPECT analysis, the sensorimotor region may be preferable to pons or cerebellum.[26]

### Statistical Analyses

Demographic, clinical, and predictor variables were compared in converters to AD, nonconverters to AD, and healthy comparison subjects by $\chi^2$ for categorical variables and Kruskal-Wallis test for categorical variables. $\chi^2$ and Fisher's exact test were

**TABLE 2. Baseline Features of 127 Patients With MCI (Converters and Nonconverters to AD During 1–9 Years of Follow-Up) and 59 Healthy Comparison Subjects**

| Features | Patients: 31 Converters Mean (SD) or % (n) | Patients: 96 Nonconverters Mean (SD) or % (n) | Healthy Comparison Subjects, 59 Subjects Mean (SD) or % (n) | Test Statistic[a] (*df*) | p |
|---|---|---|---|---|---|
| Sex: % men | 38.71 (12) | 44.79 (43) | 45.76 (27) | 0.45 (2) | 0.7984 |
| Baseline age (years) | 72.81 (6.95) | 64.48 (9.69) | 65.723 (9.49) | 18.78 (2) | <0.0001 |
| Education in years | 13.94 (4.74) | 15.44 (4.24) | 16.73 (2.61) | 7.10 (2) | 0.0287 |
| +Follow-up duration (months) | 22.84 (17.14) | 57.69 (26.81) | 64.27 (30.04) | 43.0 (2) | <0.0001 |
| Baseline MMSE | 26.19 (2.12) | 28.01 (1.96) | 29.34 (0.78) | 57.84 (2) | <0.0001 |
| Apolipoprotein E ϵ4 carrier % | 40.74 (11) | 25.53 (24) | 23.21 (13) | 3.09 (2) | 0.2137 |
| SRT total recall | 35.37 (9.31) | 45.46 (8.17) | 52.66 (6.48) | 61.39 (2) | <0.0001 |
| WAIS-R digit symbol | 32.19 (10.66) | 43.26 (12.07) | 50.64 (11.53) | 39.69 (2) | <0.0001 |
| UPSIT | 24.74 (8.90) | 33.01 (4.47) | 34.76 (4.32) | 36.36 (2) | <0.0001 |
| FAQ | 2.66 (2.22) | 1.29 (1.92) | NA | 11.49 (1) | 0.0007 |
| MRI hippocampal volume[b] | 3.78 (0.72) | 4.38 (0.63) | 4.33 (0.55) | 12.91 (2, 177) | <0.0001 |
| MRI entorhinal cortex volume[b] | 0.3709 (0.0889) | 0.4648 (0.0868) | 0.5479 (0.0984) | 39.50 (2, 177) | <0.0001 |

*Notes:* MMSE: Folstein Mini-Mental State Examination, range 0–30; SRT: Selective Reminding Test, 12-item, 6-trial version; UPSIT: 40-item University of Pennsylvania Smell Identification Test, range 0–40; FAQ: Pfeffer Functional Activities Questionnaire score, administered to informant, range 0–10.

[a] $\chi^2$ test or Kruskal-Wallis Test for three-group comparisons in categorical and quantitative variables, except for hippocampal and entorhinal cortex volumes (ANCOVA).

[b] Hippocampal and entorhinal cortex volumes are the sum of the right and left brain structures in cubic centimeter, and three-group differences were tested with ANCOVA adjusting for intracranial volume.

used to detect group differences in binary variables between MCI converters and nonconverters.

To examine the association between SPECT variables and time from baseline to AD conversion, the cumulative probability curve of AD conversion was estimated with the Kaplan-Meier product limit method and the log-rank test used to detect differences between categories. Age-stratified Cox proportional hazards models were used to examine the effect of visual rating measures, and each ROI value, on conversion to AD, with and without controlling for demographic and other baseline variables.

The false discovery rate, defined as the expected proportion of incorrectly rejected hypotheses among all rejected hypotheses, was calculated for p-value adjustment to control for the overall Type I error rate in testing hypotheses of the effect of SPECT variables in multiple ROIs.

In the 3-year follow-up sample, logistic regression models were applied to assess the predictive utility (conversion to AD) of SPECT measures associated with time to AD conversion in survival analysis. Additional logistic regression analyses to estimate risk of AD conversion included age, MMSE, and apolipoprotein E ϵ4 genotype as predictors. Sensitivity and specificity were then calculated for each value of estimated risk to form a receiver operating characteristic curve. The area under the curve was obtained to measure predictive accuracy.

## RESULTS

### Sample Characteristics

Demographic and clinical features, and predictor values, are described in Table 2. Among the 31 converters of 127 patients with MCI, 14 (11%) converted in Year 1 of follow-up, 10 (9% of the remainder) converted in Year 2, three converted in Year 3, 0 converted in Year 4, three converted in Year 5, one converted in Year 6, and 0 converted in Years 7–9. At baseline, eventual MCI converters were older and less educated, and had worse cognitive test performance, lower UPSIT scores, greater impairment in complex social and functional tasks, and smaller MR hippocampal and entorhinal cortex volumes.[3] Among healthy comparison subjects, two progressed to MCI and none progressed to AD during follow-up.

TABLE 3. Baseline Clinical SPECT Ratings of Alzheimer Disease (AD) Versus No AD (Score of 2 or 3 Versus Score of 0 or 1 on the Rating Scale) in 127 Patients With MCI

| Rating of AD in Baseline Scans (AD = 2 or 3 Versus no AD = 0 or 1 on 4-Point Rating Scale) | 31 Converters, % Rated as AD (n) | 96 Nonconverters, % Rated as AD (n) | Fisher's Exact Test, p |
|---|---|---|---|
| Lateral parietal | 19.35 (6) | 11.58 (11) | 0.3623 |
| Lateral temporal | 0 (0) | 2.17 (2) | 0.9999 |
| Medial parietal | 25.81 (8) | 14.74 (14) | 0.1780 |
| Medial temporal | 25.81 (8) | 21.74 (20) | 0.6284 |
| Global rating of AD | 41.94 (13) | 17.71 (17) | 0.0134 |
| **Rating of AD in Baseline Scans (AD = 1 or 2 or 3 Versus no AD = 0 on Rating Scale)** | | | |
| Lateral parietal | 51.61 (16) | 44.21 (42) | 0.5363 |
| Lateral temporal | 3.23 (1) | 4.35 (4) | 0.9999 |
| Medial parietal | 77.42 (24) | 67.37 (64) | 0.3698 |
| Medial temporal | 70.97 (22) | 54.35 (50) | 0.1402 |
| Global rating of AD | 80.65 (25) | 71.88 (69) | 0.4800 |

### SPECT Expert Visual Ratings

Converters (N = 31) differed from nonconverters (N = 96) in the global AD rating (p = 0.04, 42% sensitivity, 82% specificity, 43% positive predictive value, and 81% negative predictive value), but they did not differ significantly in medial temporal, lateral temporal, medial parietal, and lateral parietal regional ratings (Table 3). In survival analysis, the overall rating of no AD (0 or 1) versus AD (2 or 3) predicted time to conversion to AD (log rank test TS = 7.89, *df* = 1, p = 0.005) but not the regional ratings: medial temporal (TS = 0.40, *df* = 1, p = 0.53), lateral temporal (TS = 0.61, *df* = 1, p = 0.44), medial parietal (TS = 1.87, *df* = 1, p = 0.17), and lateral parietal (TS = 0.96, *df* = 1, p = 0.33). When the overall rating was reclassified as no AD (score of 0) versus AD (score of 1, 2, or 3), the global AD rating did not predict time to AD conversion (TS = 1.34, *df* = 1, p = 0.25).

When logistic regression analyses were conducted in the sample restricted to patients with 3-year follow-up, the results were virtually identical with the global AD rating (score of 0 or 1 versus 2 or 3) showing 41.9% sensitivity, 82.3% specificity, 43.3% positive predictive value, 81.4% negative predictive value, and all regional ratings were nonsignificant.

### Quantitative ROI Analyses

Of 194 SPECT scans conducted in patients and healthy comparison subjects, 18 scans were of insufficient quality for quantitative analyses. Reasons for exclusion were poor coregistration (N = 5), poor segmentation (N = 9), coregistration and segmentation problems (N = 2), and SPECT reconstruction issues (N = 2). The main reason underlying these coregistration and related problems was incomplete coverage of the lower brain due to interference of the gantry with the subject's shoulders; incomplete cerebellar coverage was not used as an exclusion criterion at the time of the SPECT scan (all subjects completed the scan) but led to exclusion at the time of image analysis based on the reasons specified above. Two MRI scans were of insufficient quality to permit accurate ROI tracings. Therefore, 174 subjects (115 patients and 59 comparison subjects) with both SPECT and MRI scans comprised the ROI analyses sample. Of these 115 patients with MCI, 24 converted to AD during follow-up. In patients with MCI, there were no significant correlations between the SPECT ROI measures and age, education, or baseline MMSE.

MCI nonconverters and healthy comparison subjects did not differ significantly in any ROI. When examined as continuous variables, the ROI measures did not differ significantly between MCI converters and nonconverters. When the ROIs were dichotomized at the median value in patients with MCI, the proportion with low parietal and medial temporal (hippocampus +parahippocampal gyrus) flow was significantly greater in MCI converters to AD compared with MCI nonconverters (Table 4).

**TABLE 4. Baseline SPECT ROI Measures (Ratio to Sensorimotor Cortex) in Comparisons of MCI Nonconverters and Converters to AD**

| SPECT Variable (Left + Right, <Median Value of the Patients With MCI) | Patients With MCI: 24 Converters % (n/N) | Patients With MCI: 91 Nonconverters % (n/N) | $\chi^2$ ($df$ = 1) | p | FDR |
|---|---|---|---|---|---|
| Posterior cingulate <1.73 | 54.17 (13/24) | 48.35 (44/91) | 0.0769 | 0.7815 | 0.7815 |
| Parietal cortex <1.73 | 73.91 (17/23) | 43.18 (38/88) | 5.7143 | 0.0168 | 0.0420 |
| Hippocampus (S) <1.38 | 70.83 (17/24) | 45.05 (41/91) | 4.0699 | 0.0437 | 0.0683 |
| Parahippocampal gyrus(S) <1.56 | 70.83 (17/24) | 46.15 (42/91) | 3.6949 | 0.0546 | 0.0683 |
| Medial temporal (hipp +parahipp) <2.96 | 79.17 (19/24) | 46.15 (42/91) | 7.0373 | 0.0080 | 0.0400 |

*Note:* FDR: false discovery rate.

In survival analysis using separate age stratified Cox proportional hazards models for each ROI as a predictor, baseline variables examined as continuous measures were unrelated to time to conversion: posterior cingulate (Wald test: TS = 0.15, $df$ = 1, p = 0.70), hippocampus (TS = 0.40, $df$ = 1, p = 0.53), parahippocampal gyrus (TS = 0.84, $df$ = 1, p = 0.36), and parietal cortex (TS = 1.47, $df$ = 1, p = 0.23). When these ROIs were dichotomized at their median value in patients with MCI, age-stratified Cox proportional hazards models indicated that low flow significantly increased the hazard of conversion to AD for parietal cortex and medial temporal lobe (Table 5), with stronger effects after controlling for baseline MMSE (Table 5). The survival curves for low blood flow versus high blood flow in parietal cortex and medial temporal regions are displayed in Fig. 1.

The results of the predictor analyses were essentially unchanged when restricted to patients with amnestic MCI (73% of patients). Education (number of years) was not significant when included in age-stratified Cox proportional hazards models with each ROI as a predictor and did not materially alter the results obtained in these analyses.

### Added Value of SPECT to Other Predictors

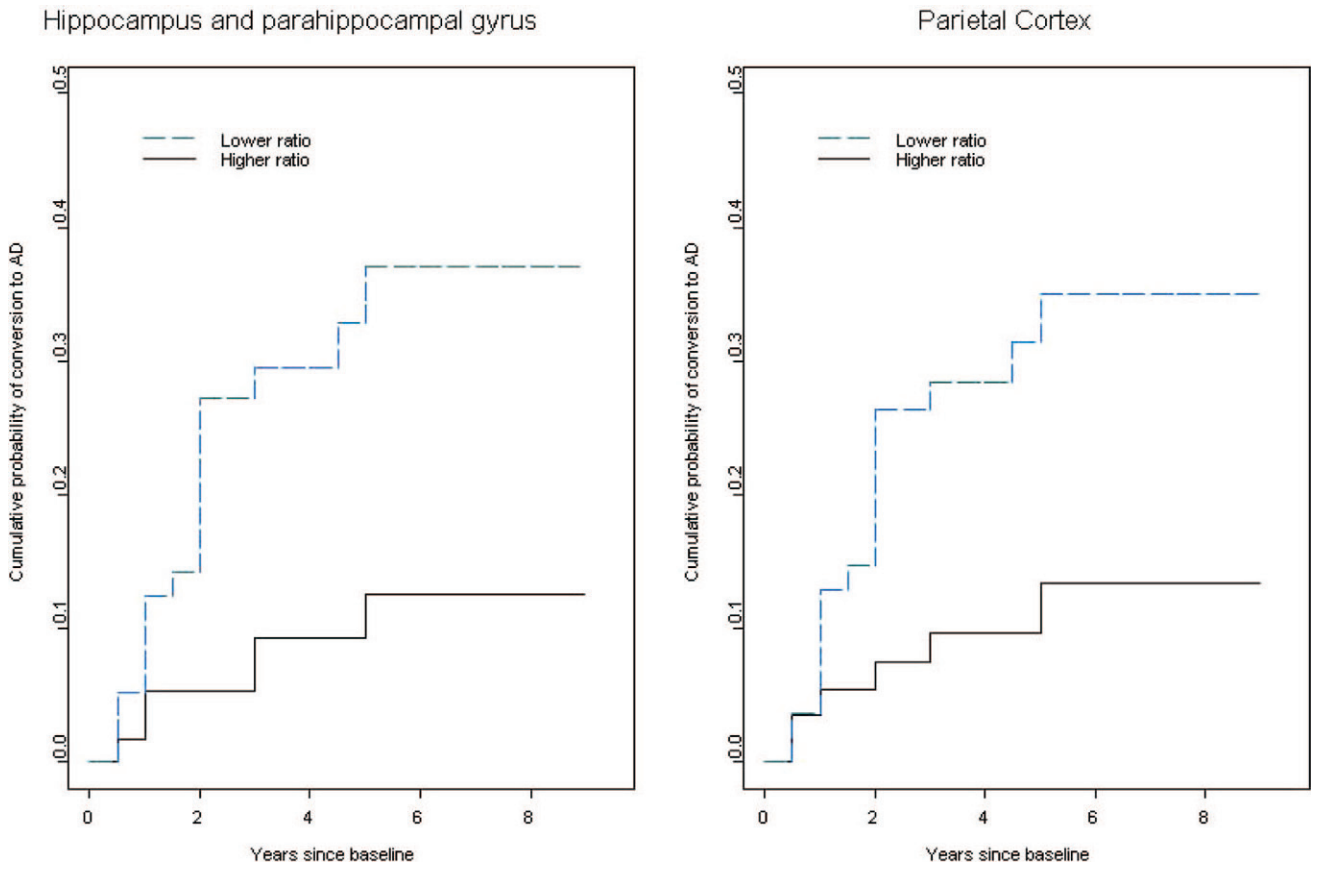
To evaluate the predictive utility of the SPECT ROI measures, receiver operating characteristic analyses were conducted in the 3-year follow-up sample for parietal and medial temporal flow (dichotomized at the median of patients with MCI) singly and combined with other predictors.[3] For low parietal and medial temporal flow as predictors of AD conversion, sensitivity was 75% and 81%, specificity was 55% and 55%, and correct classification rate was 59% and 60%, respectively. The two dichotomized measures added to some

**TABLE 5. Hazards Ratios (HRs) and 95% CI Derived From Age-Stratified Cox Proportional Hazards Models for SPECT ROI Measures Dichotomized at the Median Value of the Patients With MCI (Sensorimotor Cortex Reference), With and Without Controlling for Baseline MMSE**

| SPECT Variables | Converters/ Total | Model Without MMSE: Hazards Ratio (95% CI) | Wald Test Statistic | p | FDR | Model With MMSE: Hazards Ratio (95% CI) | Wald Test Statistic | p | FDR |
|---|---|---|---|---|---|---|---|---|---|
| Posterior cingulate <1.73 versus 1.73–3.25 | 24/115 | 1.234 (0.545–2.796) | 0.2541 | 0.6142 | 0.6142 | 1.199 (0.514–2.800) | 0.1768 | 0.6741 | 0.6741 |
| Parietal cortex <1.73 versus 1.73–2.81 | 23/111 | 2.959 (1.163–7.530) | 5.1811 | 0.0228 | 0.0680 | 3.913 (1.489–10.284) | 7.6547 | 0.0057 | 0.0180 |
| Hippocampus <1.38 versus 1.38–2.61 | 24/115 | 2.429 (0.988–5.972) | 3.7370 | 0.0532 | 0.0887 | 2.391 (0.960–5.954) | 3.5053 | 0.0612 | 0.0765 |
| Parahippocampal gyrus <1.56 versus 1.56–3.50 | 24/115 | 1.977 (0.798–6.741) | 2.1691 | 0.1408 | 0.1760 | 2.479 (0.980–6.272) | 3.6743 | 0.0553 | 0.0765 |
| Medial temporal <2.96 versus 2.96–6.07 | 24/115 | 3.121 (1.137–8.564) | 4.8809 | 0.0272 | 0.0680 | 4.197 (1.424–11.951) | 7.2156 | 0.0072 | 0.0180 |

*Notes:* p value was calculated from the Wald test statistic that has $\chi^2$ distribution with one degree of freedom under the null hypothesis of zero coefficient of the predictor in the age stratified Cox proportional hazards model. FDR: false discovery rate.

**FIGURE 1. Comparisons of Survival Curves in the 3-Year Follow-Up MCI Patient Sample (N = 98)**




SPECT medial temporal (hippocampus +parahippocampal gyrus) and parietal blood flow measures dichotomized at the median values of the patients with MCI.

extent to the AUC obtained by combining age, MMSE, and apolopoprotein E (apoE) ϵ4 (AUC increased from 0.857 to 0.881 for parietal and 0.857 to 0.911 for medial temporal measures, Table 6), and positive predictive values for parietal and medial temporal regions increased when this combination was examined (Table 6). As reported previously, a combination of five hypothesized predictors, SRT total recall, UPSIT, Functional Activities Questionnaire, hippocampal, and entorhinal cortex volume strongly predicted conversion to AD and showed high levels of sensitivity, specificity, and predictive accuracy for conversion from MCI to AD.[3] In logistic regression models in the 3-year follow-up sample that included the combination of these five predictors plus either the dichotomized SPECT parietal or medial temporal blood flow measures, parietal flow nonsignificantly increased the AUC from 0.937 to 0.956 (logistic regression Wald test: TS = 3.08, *df* = 1, p = 0.0792), and medial temporal flow nonsignificantly increased the AUC from 0.937 to 0.962 (logistic regression Wald test: TS = 3.59, *df* = 1, p = 0.0582). AUC was 0.962 when the five predictors and both parietal and temporal flow were included in the model.

### Apolipoprotein E ϵ4 Allele

An age stratified Cox model applied to the MCI sample showed that apoE ϵ4 increased the hazard of AD conversion (hazard ratio = 2.76, 95% confidence interval: 1.38–8.34, Wald test: TS = 7.05, *df* = 1, p = 0.008). In logistic regression restricted to the 3-year follow-up sample, apoE ϵ4 lost significance when the

**TABLE 6. Effects of Individual and Combined Predictors for Conversion to Alzheimer Disease (AD) in the 3-Year Follow-Up Patient Sample (n = 98) Based on Logistic Regression Analysis**

| Normalized SPECT Variable Dichotomized | Converters/ Total n | Wald Test Statistic | p[a] | AUC[b] | Sensitivity %[c] | Specificity %[c] | % Correct Classification[d] | PPV %[d] | NPV %[d] |
|---|---|---|---|---|---|---|---|---|---|
| Parietal <1.73 versus 1.73–2.81 | 20/95 | 5.1589 | 0.0231 | 0.648 | 75.00 | 54.67 | 58.95 (56/95) | 30.61 (15/49) | 89.13 (41/46) |
| Medial temporal <2.96 versus 2.96–6.07 | 21/98 | 7.3488 | 0.0067 | 0.677 | 80.95 | 54.55 | 60.21 (59/98) | 32.69 (17/52) | 91.30 (42/46) |
| Predictors in logistic regression model | | | | | | | | | |
| Age | 18/92 | 7.1359 | 0.0076 | 0.857 | 83.33 | 78.38 | 82.61 (76/92) | 58.33 (7/12) | 86.25 (69/80) |
| MMSE | | 11.0108 | 0.0009 | | | | | | |
| Apoe4 | | 3.8261 | 0.0505 | | | | | | |
| Age | 18/90 | 6.7337 | 0.0095 | 0.881 | 83.33 | 84.72 | 85.56 (77/90) | 72.73 (8/11) | 87.34 (69/79) |
| MMSE | | 11.3991 | 0.0007 | | | | | | |
| Apoe4 | | 2.6352 | 0.1045 | | | | | | |
| Parietal < 1.73 | | 5.3109 | 0.0212 | | | | | | |
| Age | 18/92 | 6.3629 | 0.0117 | 0.911 | 88.89 | 79.73 | 83.70 (77/92) | 63.64 (7/11) | 86.42 (70/81) |
| MMSE | | 10.7045 | 0.0011 | | | | | | |
| Apoe4 | | 2.6922 | 0.1008 | | | | | | |
| Medial temporal < 2.96 | | 6.8817 | 0.0087 | | | | | | |
| Age | 18/90 | 6.4371 | 0.0112 | 0.910 | 88.89 | 80.56 | 85.56 (77/90) | 72.73 (8/11) | 87.34 (69/79) |
| MMSE | | 10.4912 | 0.0012 | | | | | | |
| Apoe4 | | 2.1086 | 0.1465 | | | | | | |
| Parietal <1.73 | | 0.8257 | 0.3635 | | | | | | |
| Medial temporal <2.96 | | 3.0573 | 0.0804 | | | | | | |

*Notes:* AUC: area under receiver operating characteristic (ROC) curve; PPV: positive predictive value; NPV: negative predictive value; MMSE: 30-item Folstein Mini-Mental State Examination.

[a]p value was calculated from the Wald test statistic that has $\chi^2$distribution with one degree of freedom under the null hypothesis of zero coefficient of the predictor in logistic regression for AD conversion in 3 years.

[b]AUC was obtained based on ROC analysis using logistic model with specific predictors.

[c]The pair of sensitivity and specificity has the largest sum and smallest difference among the estimates in ROC analysis using the cutoff point in predicted risk of AD conversion estimated with a logistic model.

[d]Percent correct classification and predictive values used a threshold of 0.5 on predicted risk derived from the logistic regression models.

dichotomized parietal or medial temporal flow measures (Wald test: TS = 5.31, *df* = 1, p = 0.02 and TS = 6.88, *df* = 1, p <0.01, respectively), and age and MMSE were included in the model (Table 6).

## DISCUSSION

This is the largest single-site study that examined both SPECT visual clinical ratings and quantitative ROI analyses in predicting MCI conversion to AD. The visual global AD rating, but not temporal and parietal flow ratings, significantly predicted conversion with weak sensitivity but moderately strong specificity. Visual readings of SPECT scans are often used clinically at the MCI stage to assess likelihood of AD, but research support for this approach is very limited (Table 1). The study findings suggest that visual SPECT ratings in patients with MCI have limited utility to predict conversion to AD.

Parietal and medial temporal flow as continuous measures did not show significant predictive effects, but when dichotomized at the median value in patients with MCI, low flow in these regions predicted conversion to AD. Although medial temporal and parietal cortex flow reductions are consistent with the literature,[13,16] our negative cingulate findings are not consistent with some studies showing that posterior cingulate hypoperfusion predicts conversion to AD.[12,13]

Parietal and medial temporal flow did not add significantly to age, MMSE, and apoE ϵ4 in predicting conversion to AD by 3-year follow-up.[27] These SPECT measures also did not add significantly to the robust prediction obtained by the combination of five hypothesized predictors in this sample,[3] suggesting that the utility of SPECT may decrease when these other tests are used. This is the first study that has examined the utility of SPECT in predicting MCI conversion to AD after controlling for several other strong predictors. All

seven predictors were not assessed in all patients, and reduced sample size was a limitation in these analyses.

The ROI analyses used partial volume correction with the subject's own MRI scan that helped to address individual anatomical variability and differential regional cerebral atrophy affecting SPECT blood flow findings (Table 1). Limitations of the Strichman scanner led to incomplete brain coverage in some subjects and consequent reduction in sample size available for analysis. SPECT has lower resolution compared with PET, and this may have diminished the ability to detect differences between MCI converters and nonconverters using continuous ROI measures. The conversion rate in the MCI sample was slightly lower than that reported by others,[2,13] which may be related to the relatively broad study inclusion criteria compared with other studies restricted to patients with amnestic MCI. Of note, the SPECT findings in this study were essentially unchanged when the analyses were restricted to patients with amnestic MCI.

In a meta-analysis of MCI prediction studies using PET[28] that used quantitative or semiquantitative methods (studies of visual ratings excluded), FDG-PET showed slightly better predictive accuracy (89% sensitivity and 85% specificity) than SPECT (84% sensitivity and 70% specificity) or volumetric MR imaging (sensitivity 73% and specificity 81%). However, most PET studies included in the meta-analysis involved small numbers of subjects. Recent findings from the Alzheimer's Disease Neuroimaging Study suggest that FDG-PET has strong utility in discriminating AD, MCI, and healthy comparison subjects and may be useful in predicting MCI conversion to AD.[29]

For SPECT, published quantitative methods of analysis are not uniformly standardized, and cutoffs invariably have been derived from the data within a specific sample (as in this study). Clinical application of these quantitative methods to individual patients requires the development of standardized ratios and specific cutoff values with demonstrated consistency across studies. The performance of the predictors used in the study, particularly those derived directly from study data (median ROI uptake) need replication and is likely to be smaller in an independent second sample. Our results were obtained with the relatively high sensitivity of the dedicated head SPECT camera used, which is likely to be higher than a general purpose dual-head or 3-headed gamma camera.

From a theoretical perspective, decreased cerebral blood flow and metabolism in AD (and MCI converters to AD) may occur before neuronal loss in the disease process, may be secondary to local neuronal loss, or may reflect amyloid-related vascular pathology in the walls of blood vessels.[30] Another contributing factor may be the loss of cholinergic projections from the basal forebrain to hippocampus and neocortex.

In summary, SPECT visual ratings showed modest utility in predicting MCI conversion to AD. ROI analyses showed moderate predictive utility for parietal and medial temporal flow reductions, when dichotomized, in predicting conversion to AD. The value of SPECT in predicting MCI conversion to AD is modest and may decrease when other, less expensive predictors are available.

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