# Regional HmPAO SPECT and CT Measurements in the Diagnosis of Alzheimer's Disease

*A. Mattman, H. Feldman, B. Forster, D. Li, I. Szasz, B.L. Beattie and M. Schulzer*

**ABSTRACT:** ***Background:*** This study investigated the hypothesis that the combination of regional CT brain atrophy measurements and semiquantitative SPECT regional blood flow ratios could produce a diagnostic test for Alzheimer's disease (AD) with an accuracy comparable to that achieved with the present clinical gold standard of the NINCDS-ADRDA criteria. ***Methods:*** Single proton emission computed tomography (SPECT) and CT head scans were performed on 122 subjects referred an UBC Alzheimer clinic and diagnosed as either 'not demented' (ND-37) or 'possible/probable AD' (AD-85) by the NINCDS-ADRDA criteria. Stepwise discriminant analysis (SDA) was performed on the bilateral SPECT regions of interest and compared to bilateral CT qualitative/quantitative assessment in the frontal, parietal and temporal lobes to determine which were most accurate at ND/AD distinction. Receiver operating curves (ROC) were then constructed for these variables individually and for their combined discriminant function. ***Results:*** The left temporal qualitative cortical atrophy score (CT) and left temporal perfusion ratio (SPECT) were selected in the SDA. The combined discriminant function was more specific at AD/ND distinction than either of CT or SPECT alone. The accuracy of AD/ND distinction with the combined discriminant function was below that achieved by clinical diagnosis according to the NINCDS-ADRDA criteria and was not significantly different from that achieved with SPECT or CT alone as defined by ROC curve analysis. ***Conclusion:*** The measurements of left temporal cortical atrophy and regional cerebral blood flow were most indicative of AD; however they lacked the sensitivity and specificity to recommend their use as a diagnostic test for AD.

**RÉSUMÉ: Scintitomographie régionale au HmPAO et mesures par CT scan dans le diagnostic de la maladie d'Alzheimer.** ***Introduction et objectifs:*** Dans cette étude nous évaluons l'hypothèse selon laquelle l'association de mesures de l'atrophie cérébrale régionale par CT scan et de rapports de débits sanguins régionaux obtenus par SPECT pourrait constituer un test diagnostique de la maladie d'Alzheimer (MA) d'une précision comparable à celle des critères de l'étalon or actuel, le NINCDS-ADRDA. ***Méthodes:*** 122 patients référés à la clinique d'Alzheimer de l'Université de la Colombie-Britannique ont subi un scan cérébral par SPECT et par CT, et on les a classifiés comme non déments (ND-37) ou MA possible/probable (MA-85) selon les critères du NINCDS-ADRDA. Nous avons effectué une analyse factorielle discriminante pas à pas (ADP) sur les données des régions d'intérêt obtenues par SPECT bilatéral et nous l'avons comparée à l'évaluation qualitative/quantitative des lobes pariétaux et temporaux bilatéraux obtenue par CT afin de déterminer quelle méthode d'investigation était plus fiable pour distinguer les patients ND des MA. Des courbes ROC ont ensuite éte générées individuellement pour ces variables et pour leur fonction discriminante combinée. ***Résultats:*** La cote d'atrophie corticale qualitative du lobe temporal gauche (CT) et le taux de perfusion du lobe temporal gauche (SPECT) ont été sélectionnés à l'ADP. La fonction discriminante combinée était plus spécifique pour distinguer la MA de la ND que le CT ou le SPECT seul. La précision de la distinction MA/ND au moyen de la fonction discriminante comtinée état inférieure à celle obtenue par le diagnostic clinique selon les critères du NINCDS-ADRDA et n'était pas significativement différente de celle obtenue par le SPECT ou le CT seul, selon l'analyse de courbe ROC. ***Conclusions:*** Les mesures de l'atrophie corticale du lobe temporal gauche et du débit sanguin cérébral régional étaient les meilleurs marqueurs de la MA; cependant, ils n'ont pas une sensibilité et une spécificité suffisante pour recommander leur utilisation comme épreuves diagnostiques de la MA.

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The imaging of cerebral blood flow and metabolism using emission tomography has been a powerful investigative tool for the dementias.[1-4] Positron emission tomography (PET) studies have demonstrated patterns of regional decreased cerebral glucose metabolism[3] and blood flow[1-4] in AD. Similarly, single photon emission computed tomography (SPECT) studies in AD using the radionuclide 99mTc HmPAO have demonstrated characteristic regional patterns of decreased cerebral blood flow.[5-7] The abnormal pattern of regional CBF considered characteristic of AD is a bilaterally decreased perfusion to the temporal and parietal lobes.[5,7-11] This pattern can be seen in other neurodegenerative disorders including Parkinson's Disease[12,13] and vascular dementia.[14]

The significance of assymetrical and unilateral perfusion abnormalities in AD has been debated. Several studies have

From the Clinic for Alzheimer's Disease and Related Disorders, Vancouver Hospital and Health Sciences Center-UBC Site (A.M.); Clinic for Alzheimer's Disease and Related Disorders, Division of Neurology, Department of Medicine, Vancouver Hospital and Health Sciences Center-UBC Site (H.F.); Clinic for Alzheimer's Disease and Related Disorders, Division of Geriatric Medicine, Department of Medicine, Vancouver Hospital and Health Sciences Center-UBC Site (B.L.B.); Department of Radiology, Vancouver Hospital and Health Sciences Center (B.F., D.L.); Department of Nuclear Medicine, Vancouver Hospital and Health Sciences Center-UBC Site (I.S.); Departments of Statistics and Medicine, Vancouver Hospital and Health Sciences Center (M.S.) Vancouver.

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*Reprint requests to:* Dr. Howard Feldman, Division of Neurology, Vancouver Hospital and HSC-UBC Site, S192-2211 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 2B5

demonstrated that right left asymmetries of regional cerebral metabolism with PET[15-17] is a significant feature of AD. Left hemispheral perfusion decreases have been found to be more significant with respect to probability of AD as well as in correlating to the dementia severity.[9,18,19] Not all studies however have noted these associations.[20-22] The question of the relative importance of asymmetrical and left sided SPECT perfusion abnormalities in AD requires further clarification and investigation.

By contrast, the role of computed tomographic (CT) head scanning in positively identifying AD has been limited. CT scanning has found its diagnostic place in identifying treatable or comorbid pathology in dementia patients. However, the positive diagnosis of AD via CT has been limited due to overlap of atrophy measures between cognitively normal individuals and patients with AD.[23-29] Recently, several studies have demonstrated that certain regional CT atrophy measurements may play an important role in the assessment of AD. Measurements of the degree of temporal lobe atrophy in particular have been shown to be both sensitive and specific in the identification of AD.[24,28,30-37] De Leon et al.[34] reported a sensitivity of 91% and a specificity of 89% of diagnosing AD as compared to normal controls when using a quantitative medial temporal width measure as an indicator of AD. However, these measurements involve complex methodologies for volumetric measurement or are taken from CT scans obtained in a non-standard manner. They have remained largely restricted to research settings.

There have been reports of potential advantages of combining both SPECT and CT information in the investigation of AD. In the OPTIMA project[38] SPECT was combined with CT whereas Pearlson et al.[20] combined SPECT with MRI, to describe a highly characteristic pattern for AD of atrophy of the medial temporal lobe combined with perfusion defects in the ipsilateral superior temporoparietal regions. These studies reported improved diagnostic levels of sensitivity and specificity over unimodal studies. The combination of regional SPECT and CT information as a potential practical diagnostic tool for AD requires further investigation in a large AD clinic population.

In the present study regional CT and SPECT variables were combined to investigate the accuracy of distinguishing AD from ND beyond the ability of each modality alone. The sensitivity and specificity of HmPAO SPECT semiquantitative perfusion ratios in identifying AD was compared to the assigned clinical diagnosis of a dementia referral clinic team. Lateralized variables were developed in order to elucidate differences between left and right sided findings in AD. Cortical regions which best distinguished AD from ND patients utilizing regional SPECT perfusion ratios and regional CT atrophy measurements were determined.

## Methods

**Subjects:** Between March 1990 and July 1992 there were 197 consecutive patients seen at the UBC Clinic for Alzheimer's Disease and Related Disorders for the evaluation of cognitive symptoms/dementia. Patients diagnosed as "possible AD" (n=64), "probable AD" (n=79), or "not demented (ND)" (n=54) according to the NINCDS-ADRDA work group criteria[39] were considered for this study. All patients underwent a detailed medical and neurological evaluation, a uniform neuropsychological test battery, CT head scan and HmPAO SPECT scanning. Laboratory investigations included CBC, ESR, $B_{12}$, folate, serology for syphilis, thyroid hormone levels and liver function studies. Additional lab investigations were obtained as clinically indicated to ensure that there were no additional modifiable / reversible disorders. A diagnosis of dementia was assigned according to DSM III-R.[40] Dementia severity was assessed and scored with the multidimensional Functional Rating Scale (FRS).[41,42] Patients were diagnosed as "probable AD" (n=79) "possible AD" (n=64), or "not demented (ND)" (n=54) according to the NINCDS-ADRDA criteria.[39]

The ND group included those referred patients who following Clinic assessment were classified as not meeting the criteria for AD or any other dementia. These patients were not assigned a further diagnosis such as AAMI[43] or cognitively impaired not demented (CIND).[44] A diagnosis of "possible AD" was assigned to patients who met criteria for "probable AD" but who had comorbid medical diseases, significant extrapyramidal features, or risk factors for alternative causes of dementia. To guard against the inclusion of vascular dementia patients in the AD group patients with ischemic regions on CT were removed from the study if the lesions corresponded to regions of hypoperfusion on SPECT. Those patients whose scans for technical reasons were of poor quality (either CT/SPECT or both) were excluded from further analysis. One hundred seventy-six subjects remained in the study after these exclusion criteria were applied (Table 1a). Additionally those patients whose CT head scans could not be obtained for review or whose studies had been performed more than 6 months prior to their clinical assessment, were also excluded, leaving 122 patients who were fully evaluable (Table 1b).

**SPECT Methods and Analysis:** The HmPao was supplied as a freeze dried mixture reconstituted with 99mTc-Pertechnetate solution. A dose of 10 - 15 mCi was injected intravenously within 10 minutes of preparation. During injection patients lay in a dark quiet room with a towel over their eyes.

**Table 1a:** Demographic Data for Patients with SPECT Perfusion Ratios.

| | Total (SD) | ND (SD) | AD (SD) |
|---|---|---|---|
| N | 176 | 48 | 128<br>55 Poss 73 Prob |
| Sex | 69M 107F | 21M 27F | 48M 80F |
| Mean Age | 69 (9) | 65 (11) | 70 (8) |
| Mean Total FRS | 24 (6) | 17 (4) | 26 (5) |

(SD = standard deviation)
("poss" = possible AD, "prob" = probable AD)

**Table 1b:** Demographic Data for Patients with CT Atrophy Measurements.

| | Total (SD) | ND (SD) | AD (SD) |
|---|---|---|---|
| N | 122 | 37 | 85<br>poss 36 prob 49 |
| Sex | 46M 76F | 15M 22F | 31M 54 F |
| Mean Age | 69 (9) | 66 (11) | 70 (8) |
| Mean Total FRS | 23 (6) | 17 (4) | 26 (5) |

(SD = standard deviation)
("poss" = possible AD, "prob" = probable AD)



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Imaging commenced 15-60 minutes after injection. Patients were scanned with the Siemens ZLC 3700 orbiter single-headed gamma camera system with resolution of 20 mm full width at half maximum in the plane of the reconstructed image. The patient's head was positioned in a moulded plastic headrest so that the inferior orbital rim was perpendicular to the camera face. The head was stabilized with tape to maintain the anatomical position. The camera rotated about the subject's head in 64 steps imaging for 30 seconds at each position. Raw counts were stored in a computer using a 64 x 64 pixel matrix. Tomographic slices were reconstructed without attenuation correction to produce a series of 1 pixel (6.5 mm) thick axial slices. This yielded an average of 35 slices for each brain. Average counts per pixel were measured. Coronal and/or sagittal images were reconstructed to construct a three dimensional display of the brain at any level. The reconstructed images were evaluated by nuclear medicine physicians who had no clinical information excepting that the patient had been referred from the Clinic for a dementia evaluation. Visually identified regions of hypoperfusion (ROIs) of at least 20 pixels were noted by the radiologist. Irregular regions of interest (ROIs) were placed over the areas of hypoperfusion in the parietal, posterior temporal, and frontal lobes as well as the cerebellum as previously reported by Hurwitz et al.[45] from the same unit. If the region appeared normal visually, the greater part of each specified region was outlined. Left and right ROIs for each patient were identical but differed between patients. The cerebellar ROI was drawn to encompass both cerebellar hemispheres. ROI standardization was attempted by computing a ratio of the cortical/cerebellar ROIs. The cerebellum was used as its blood flow is usually normal in Alzheimer's disease.[7] Using the irregular cortical/cerebellar ROI ratio, a ratio of greater than 0.86 had been established as the normal control value.[45] A cutoff of ≤ 0.85 was used to identify abnormal regions of hypoperfusion. Previously irregular ROIs as well as regular ROIs of 36 pixels had been studied in this way.[45]

**CT Analysis:** Non-contrast axial cranial CT scans were performed on all subjects in the study. The scan angle was parallel to the orbitomeatal line. Of the 122 CT scans that were available for review (Table 1b) and analysis, 93 were done at the University Hospital with a Seimens DR-H whole body scanner. Contiguous 8mm sections were obtained from skull base to vertex. The remaining CT scans were taken at outside hospitals and the slice thickness varied from 5mm to 10mm. Twelve different measures of atrophy were taken from each head scan including six linear ratio measures of central atrophy and six qualitative measures of cortical atrophy.

**Linear Ratios:** Three linear ratios were calculated for each hemisphere of the brain. These ratios are variations of well known measures described in the literature which have been shown to be significantly different in AD as compared to normal controls.[30,46-49] The suprasellar cistern width ratios[50] were used as measures of left and right temporal atrophy. The anterior horn ratios (AHR)[51] were used as measures of left and right frontal lobe atrophy. The lateral ventricular width ratios (LVWR)[30] were used as measures of left and right parietal lobe atrophy.

**Qualitative Measures:** Subjective estimates of cortical atrophy were made in the frontal, temporal and parietal lobes bilaterally. Atrophy in each region was graded on a score of 0-3 where 0 indicated no atrophy and 3 indicated marked atrophy. A reference scan for each grade of atrophy was provided to the reviewing radiologist. Two radiologists assessed each CT scan independent of one another and were blind to information from the SPECT scans as well as clinical information other than the age of the patient.

**Statistical Analysis:** Analysis of data included discriminant classification, receiver operating curve (ROC) analysis, paired t-tests, and Steiger's test for comparing two correlated correlation coefficients.[52]

## Results

**Classification Ability of SPECT:** The group of 176 patients with SPECT data were first classified as AD or ND patients on the basis of either a bilateral temporal or bilateral parietal abnormal SPECT perfusion ratio. This method correctly identified clinically diagnosed AD with a sensitivity of 53.9% and a specificity of 75.0% (Table 2). When the criteria for AD SPECT diagnosis were adjusted to include the presence of either a unilateral or bilateral temporal or a unilateral or bilateral parietal abnormal perfusion ratio, the sensitivity increased to 78.9% while specificity decreased to 64.6%. The bilateral perfusion ratios of the frontal, temporal, and parietal lobes were all significantly more asymmetrical in the AD group as compared to the ND group ($p<0.01$ for all t-tests).

**Table 2:** Prevalence of SPECT Perfusion Abnormalities by Group.

| | AD (128) | ND (48) | PPV | NPV |
|---|---|---|---|---|
| Bilat T/P | 69 (53.9%) | 12 (25.0%) | 85.2% | 62.1% |
| Uni or Bilat T/P | 101 (78.9%) | 17 (35.4%) | 85.6% | 46.6% |

(Bilat T/P - bilateral perfusion ratio <0.86 of either temporal or parietal lobes or both)

(Uni or Bilat T/P - uni or bilateral perfusion ratio <0.86 of either temporal or parietal lobe or both)

(PPV - positive predictive value, NPV - negative predictive value)

### Identification of Most Relevant SPECT and CT Variables

***SPECT:*** A stepwise discriminant analysis (SDA) was used to determine which perfusion ratios were most useful in classifying the patients into the AD versus the ND groups. The left temporal (TL) perfusion ratio alone was selected ($p<0.05$). The jackknife discriminant classification of the TL variable produced a sensitivity of 60.2% with a specificity of 66.7%.

***CT:*** Grading of the CT cortical atrophy of 122 subjects was performed by two independent radiologists (BF, DL). The correlation coefficients for the two radiologists in each of the six lobes varied between 0.70 and 0.89 (kappa 0.57 to 0.76). Subsequent CT data analysis was performed using the data from the first radiologist (BF).

SDA revealed that left temporal cortical atrophy (CORLT) was the most important of the CT variables in distinguishing AD from ND patients ($p<0.05$). None of the linear measures of central atrophy were selected in the analysis. The jackknife discriminant classification of the CORLT variable produced a sensitivity of 91.8% with a specificity of 48.6% (N=122).

**Discriminant function analysis with SPECT and CT variables:** A discriminant function analysis to separate AD from ND patients was performed using the six SPECT perfusion ratios, the six qualitative CT cortical atrophy scores, and the six quantitative linear measures of central atrophy. The two statistically significant variables selected in the discriminant analysis


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were CORLT and TL (Table 3). The function derived from the linear combination of the CORLT and TL variables [COMB = (0.78997*CORLT) + (–0.48785*TL)] produced a jackknife discriminant classification with a sensitivity of 70.6% and a specificity of 75.7% (Table 4).

**Table 3:** Significance of Univariate F ratio for Discriminant Function.

| | LF | RF | LP | RP | LT | RT |
|---|---|---|---|---|---|---|
| SPECT(ROI) | 0.2916 | 0.6237 | 0.8691 | 0.6991 | 0.0086* | 0.9331 |
| CT (qual) | 0.3319 | 0.3319 | 0.3634 | 0.5148 | 0.0000* | 0.4268 |

*Variables meeting criteria for entry into Discriminant Analysis (LF=left frontal, RF=right frontal, LP=left parietal, RP=right parietal, LT=left temporal, RT=right temporal)

**Table 4.** Classification of AD Clinic Population via SDA Established Criteria.

| | N | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| TL | 176 | 60.2 | 66.7 | 82.8% | 61.4% |
| CORLT | 122 | 91.8 | 48.6 | 80.4% | 28.0% |
| COMB | 122 | 70.6 | 75.7 | 87.0% | 47.2% |

(PPV - positive predictive value, NPV - negative predictive value)

ROC curves were applied to each of the TL, CORLT and COMB variables to compare their discriminative abilities (Figure 1). The areas under the ROC curves were 0.70 for TL (SE 0.05), 0.76 for CORLT (SE 0.05), and 0.80 for COMB (SE 0.05). The area under each individual ROC curve was significantly larger than 0.5 ($p < 0.05$). Though the COMB variable had a greater area under the curve this difference was not statistically significantly different as compared to either the CORLT variable alone (p=0.40) or the TL variable alone (p=0.16).

**Correlations of SPECT Perfusion Ratios with Dementia Severity:** The six SPECT perfusion ratios each had a significant negative correlation with the total FRS score ($p < 0.05$) (Table 5). The left sided temporal, frontal and parietal ratios each had negative correlations of magnitudes larger than the corresponding right sided values; however, the relative magnitudes of the corresponding left and right sided correlation coefficients were not significantly different (Steiger's test p=0.31 for temporal lobe).

**Table 5:** Correlations between SPECT ROI and Total FRS score in AD.

| N=128 | Left | Right |
|---|---|---|
| Temporal | –0.431 | –0.387 |
| Parietal | –0.379 | –0.266 |
| Frontal | –0.341 | –0.249 |

p<0.005 (2-tailed significance)

## Discussion

**SPECT:** The clinical criteria of the NINCDS-ADRDA have been previously validated to have a diagnostic sensitivity of 80-100% with specificity 73-100%.[53-55] In applying these clinical diagnostic criteria as the "gold standard" in the present study only 53.9% of AD subjects had the described characteristic bilateral temporal or bilateral parietal SPECT perfusion defects of AD. The diagnostic sensitivity of bilateral defects for AD would clearly be quite low and of limited utility diagnostically. An additional 25.0% had either a unilateral temporal or unilateral parietal perfusion defect improving the diagnostic sensivity to 78.9% while having an associated decrease in specificity to 64.6% from 75%.

These diagnostic sensitivity values for regional CBF are consistent with some prior reports.[14,22,56,57] In a prospective study of over 100 patients with complaints of memory or cognitive

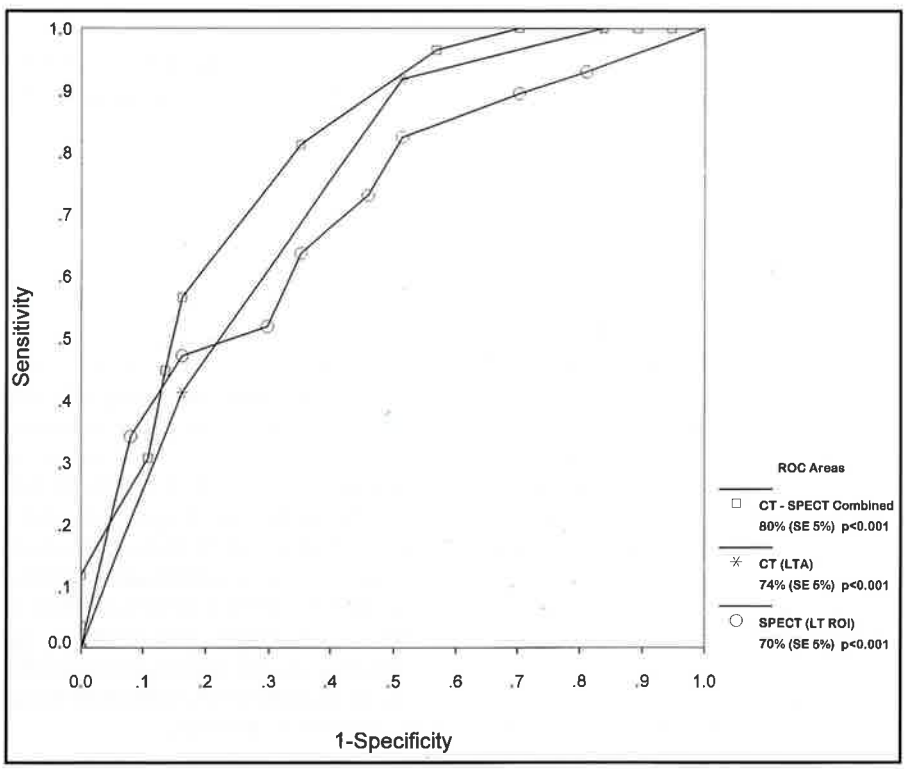


*Figure 1: ROC Curves.*



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impairment Holman[56] noted that 65% of AD patients had bilateral posterior association cortex defects and a further 15-20% had unilateral defects. Other studies have reported improved diagnostic sensitivity for regional CBF SPECT. Johnson et al.[58] achieved a sensitivity of 91% with a specificity of 86% in a smaller AD study group (n=29) and with a more complex method of automated quantitative analysis. Jobst et al.[38] achieved a histopathologically confirmed sensitivity of 96% with a specificity of 89%. However in that study the AD group was small (n=45) and subjects died largely within two years of the SPECT scans, suggesting an important effect of disease severity on the study results.

The specificity values obtained in the present study are lower than values obtained in other SPECT studies where a specificity of about 80-90% would be anticipated for a comparable level of sensitivity.[38,57,58] The discrepant specificity results would be partly attributable to the control group chosen for this study. This study set out to determine if SPECT could reliably distinguish those individuals with clinically diagnosable AD from those who were not demented according to formal research criteria. The ND group referred for the assessment of neurobehavioral symptoms included individuals without objective cognitive deficit, those with cognitive deficits not predictive of developing AD[59,60] as well as those in the incipient stages of AD short of meeting clinical criteria. Tuokko et al.[59] previously reported that 40% of such a not demented group from the same clinic were found at 12-18 month longitudinal followup to meet the clinical criteria for "clinically probable" or "possible" AD. Some of the incipient AD individuals in the control group would have consequently been anticipated to have temporoparietal SPECT abnormalities lowering the specificity of SPECT perfusion ratios in the diagnosis of AD. Nevertheless, the comparison of AD to ND clinic patients provides a more realistic clinical scenario for the evaluation of SPECT than does its use in comparing AD to a cognitively normal control group.

**CT/ SPECT Variables Most Relevant to the Identification of AD:** Of the variables that were used in the discriminant analysis the qualitative CT measures performed better in accurately classifying subjects as AD or ND than did the SPECT perfusion ratios or the quantitative CT measures. CORLT was the most useful CT variable while TL was the most useful SPECT variable in distinguishing the two groups of patients. The CORLT variable had greater diagnostic sensitivity than the clinical diagnosis but its specificity for AD was very limited. The TL perfusion ratio had better specificity than CORLT but was far less sensitive.

**SPECT and CT Combined:** The combination of CT (CORLT) and SPECT (TL) data increased the accuracy of classification of AD patients in a dementia clinic referral population over that achieved with CORLT or TL data alone. This result can be attributed to the fact that the COMB variable was created in a retrospective manner to maximally distinguish between the two groups of subjects. The COMB variable had a much greater specificity but a much lower sensitivity than the CORLT variable alone. The increase in specificity achieved by the addition of SPECT data to CT data indicates that the two modalities can be complementary.

There also appears to be strong overlap between the information obtained from the SPECT and CT data. For example, the difference between the COMB variable's discriminating ability and that of either the CORLT or the TL variables', as measured by area under the respective ROC curves, is not statistically significant. This overlap may be the result of regional atrophy. Chawluk et al.[61] and Tanna et al.[32] have previously determined that apparent differences between AD and normal control subjects, in PET measured cerebral metabolic rates, became insignificant when cerebral atrophy corrections were applied. Therefore, although SPECT and CT do complement one another as diagnostic tools in identifying AD, the overlap between the two modalities appears to be too large to justify the routine use of both for diagnostic purposes.

**Laterality of SPECT and CT findings:** The selection of temporal lobe related variables by the stepwise discriminant function would be anticipated from prior histopathologic and functional imaging studies.[22,37,62-64] However, the left sided nature of these variables is of interest in that previous studies have noted relationships between AD and the presence of asymmetrical regional cerebral abnormalities.[9,15-19] In this study, the left sided temporal variables were found to be of greater import in distinguishing AD from ND subjects. The perfusion ratios of the temporal, parietal and frontal lobes were all found to be significantly more asymmetrical in the AD patients as compared with the ND patients. Additionally, the left sided temporal perfusion ratios had a numerically larger correlation with the severity of dementia (as measured by total FRS score) than did the corresponding right sided ratios though this relationship was not statistically significant. The relatively stronger correspondence of the left sided variables with dementia severity was noted for both the frontal and parietal lobes. These results suggest the possibility that the left hemisphere is affected more severely and/or sooner than the right hemisphere in AD and has a greater role in the cognitive disease effects.

## Conclusions

1) The most useful SPECT and CT variables in the identification of AD are the temporal perfusion ratios and the temporal cortical atrophy scores respectively. The left hemispheric derived variables are potentially more indicative of the presence of AD than the right hemispheric variables.

2) SPECT and CT variables complement each other as diagnostic aids in AD. Specifically, the combination of CT and SPECT information provides a more specific identifier of AD than either modality alone. However, the overlap between the two modalities in AD appears to be too large to justify the routine use of both for diagnostic purposes.

3) The not demented group of referred subjects is heterogeneous and includes individuals at high risk for meeting AD diagnostic criteria as well as those at much lower risk. Their fractionation within the not demented group would be important in further addressing the potential value and importance diagnostically of abnormal SPECT rCBF measures. Further research in this area would be warranted but the results of this study indicate that regional SPECT perfusion ratios alone, or combined with regional CT atrophy measurements, have a poor specificity in differentiating AD subjects from clinically not demented subjects who have cognitive or behavioural symptoms possibly indicative of a preclinical dementia.



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