

A Novel Fractal Analysis of Brain PET and SPECT Distinguishes Early Dementia from Mild Cognitive Impairment in Insulin Resistant Patients.

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Background: Mild cognitive impairment (MCI) and dementia are of increasing importance in insulin resistant (IR) patients.

Methods: Basal and perfusion-stimulated brain scans used Siemens e.cam SPECT or ECAT Exact 47 PET (MiE-Scintron) for metabolic, perfusion and flow reserve indices (CMi, CPi, FRi). Modified fractal analysis used average activity, A within isocontours, I = percentages of maximal activity, M. The positive slope, S of $\ln(A)$ vs. $\ln(I)$ graphs is analogous to the negative slope, D, the fractal dimension, using $\ln(V)$, with V = voxels within each isocontour instead of $\ln(A)$.

Results: Among 41 near normal patients, $M = 2.50 \pm 0.17$ times average white matter activity and average CMi $(59.5 \pm 4.6)\% = CMA$, which helped normalizing A to $AN = (A/M)$ raised to power (CMA/CMi) . $\ln(AN)$ vs. $\ln(I)$ graphs intercept zero with slope, SN, whose values near the intercept agreed within 10% for PET or SPECT in individual patients. Patients age (60.2 ± 17.9) years, near normal ($n = 11$), or with IR and MCI ($n = 15$) or early dementia ($n = 7$), respectively had CMi $(71.1 \pm 4.4)\%$, $(58.1 \pm 8.6)\%$, $(46.8 \pm 8.3)\%$; FRi $(3.90 \pm 3.64)\%$, $(0.43 \pm 6.5)\%$, $(-0.19 \pm 3.74)\%$ and average SN (of basal and perfusion-stimulated values): 0.347 ± 0.053 ; 0.586 ± 0.086 ; 0.930 ± 0.155 . Analysis of FRi and/or ratios of CPi/CMi may also be effective; however, SN values are more precise, and distinguish MCI from early dementia ($p < 0.001$) even better than S ($p < 0.01$) or FRi ($p = 0.8$).

Conclusions: The modified fractal slope, SN, is the best single parameter we have found to distinguish early dementia from MCI in IR patients.

1.

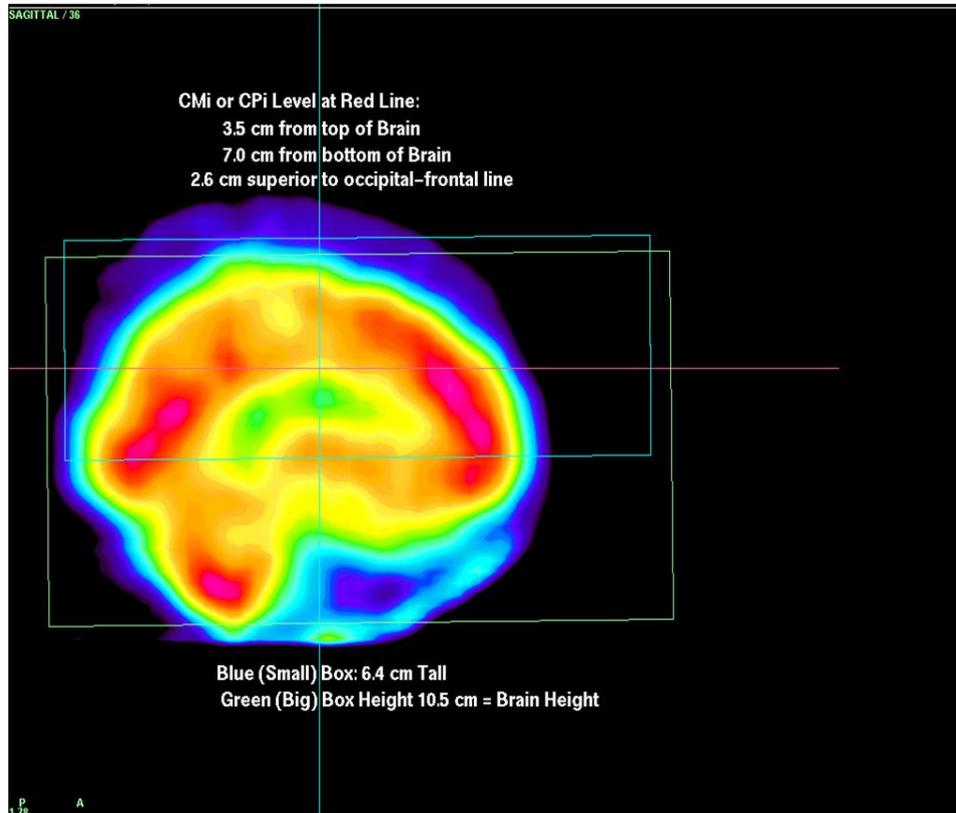


Fig. 1A. Axial SPECT slices are defined parallel to the brain long axis from occipital to prefrontal. For the Cortical Metabolic index (CMi), one or more axial slices are centered one third of the way from the top of the brain, just superior to the roof of the normal-sized lateral ventricles. Activity display uses a Sokoloff color scale, with white for peak brain, black for zero and spectral colors for intermediate activities. Computer-selected isocontours (see Fig. B) define areas that contain activity > a certain fraction of the peak activity. The 30% isocontour represents total brain activity in an axial slice, chosen slightly outside the actual external edge of the brain to correct for attenuation. The 60% isocontour approximates the cortex. The Cortical Metabolic index (CMi), the ratio of activity within the 60% isocontour to that within the 30% isocontour is a measure of cortical brain function. The Cortical Perfusion index (CPi) is similarly calculated from 60% and 30% isocontours after the patient receives a cerebral perfusion stimulant such as 0.5 to 1 g acetazolamide IV or 0.4 to 0.8 mg nitroglycerin sublingual. The difference between CPi and CMi is a measure of cerebral flow reserve (CFi).

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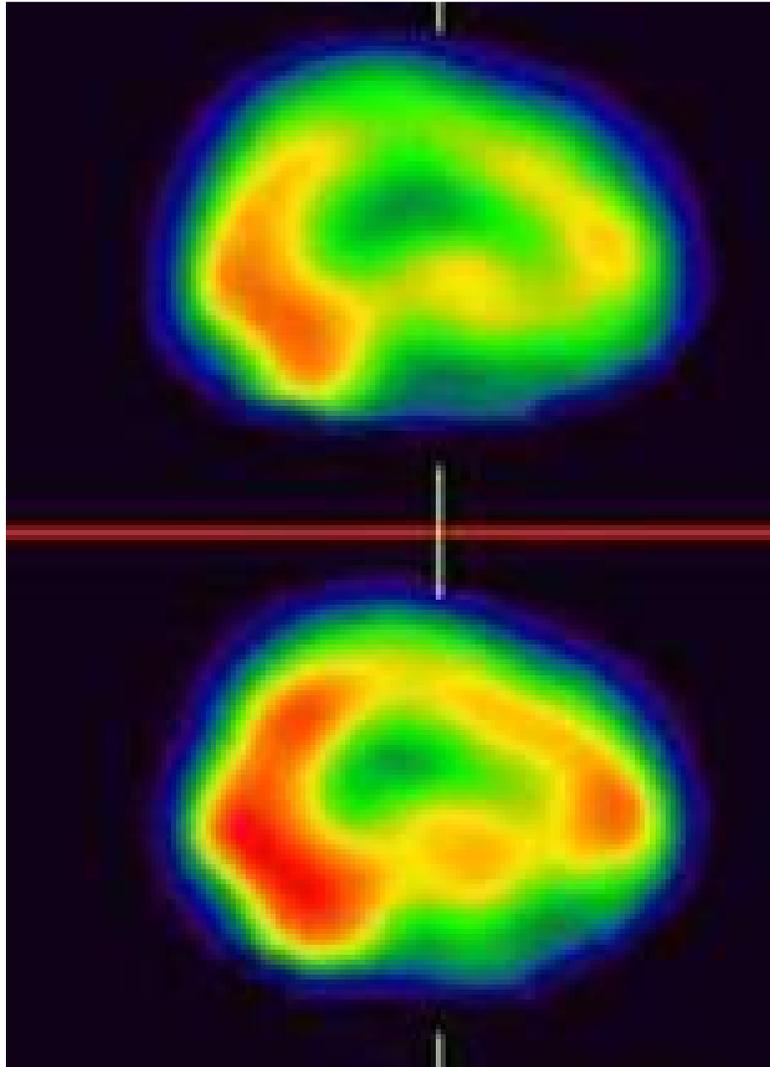


Fig. 2: A 50 year-old bipolar woman with insulin resistance (HbA1c 6.0% at 9 months before her SPECT scan) refused therapy and recently developed uncontrolled type 2 diabetes mellitus with HbA1c 11.2%. Her basal scan (2B, sagittal section shown) is remarkably normal in appearance but she has marked deficit in parietal activity in the stimulated scan (2A, corresponding sagittal image) using a mixture of medium chain triglycerides and eicosapentaeneic acid as the stimulus. Her CMi 59.5% is precisely mid normal as compared to 41 near normal patients with CMi (59.5+-4.5)%. Age 52+-14 years; however, her CPI of 45.69% is remarkably reduced vs. the 41 near normal patients CPI (69.7+-5.3)% as was her cerebral flow reserve index of -13.81% compared to the near normal patients (10.5+-5)%. The SN values were compatible with early vascular dementia and remarkably picked up the abnormality for both the basal metabolic SN 0.877 and the stimulated perfusion SN 0.958 studies comparable to SN 0.95+-0.15 for 9 patients with early dementia. It is likely that the dementia developed within the last 6 months associated with the rapid diabetic decompensation.

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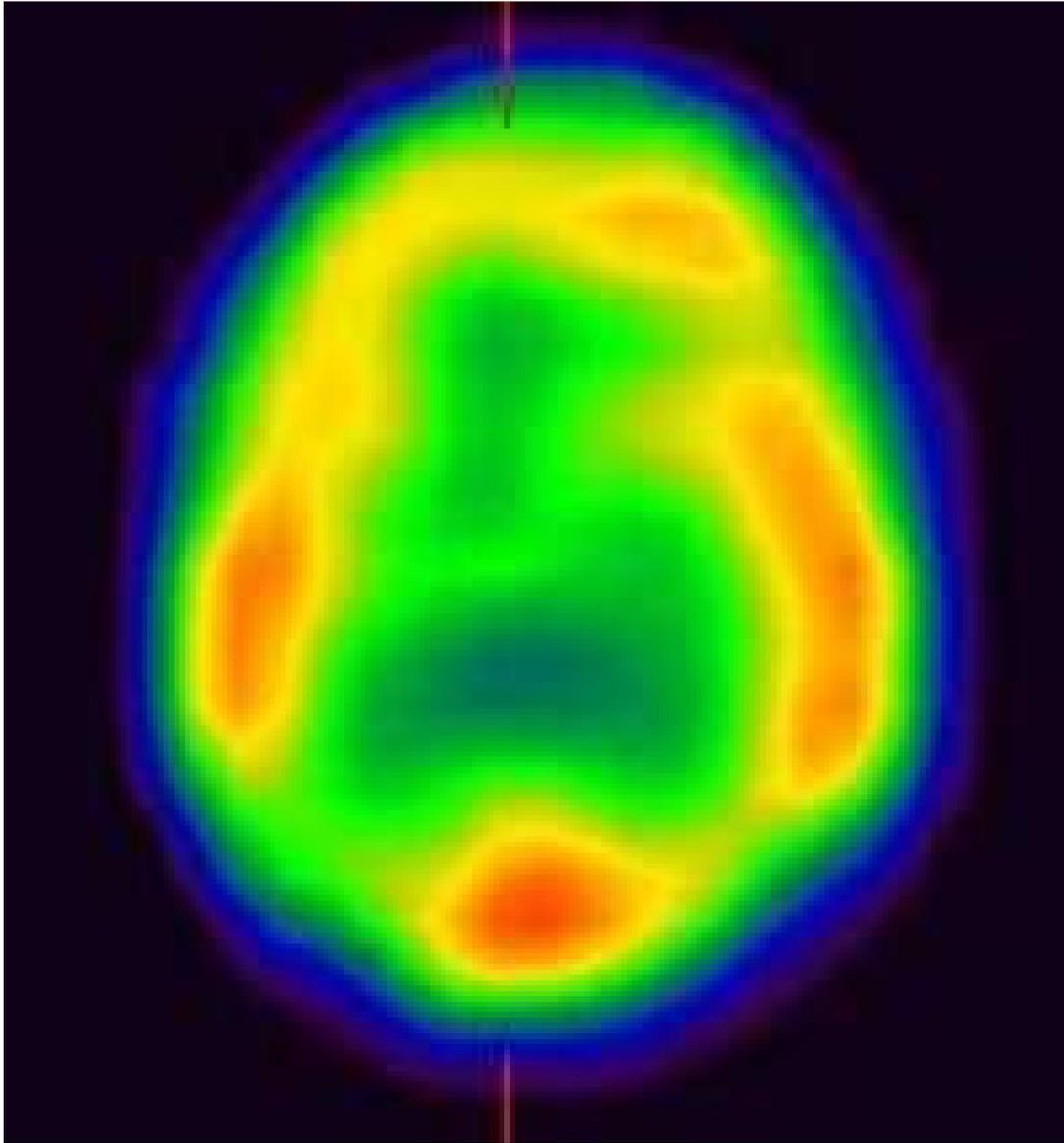


Fig 3. A 21 year-old insulin resistant woman had traumatic brain injury in a motor vehicle accident and has mild cognitive impairment with TYM 41/50 and Montreal Cognitive Assessment 23/30. Her initial SPECT scan (Fig. 3A) showed CMi 71.5% and CPi 70.22% without significant deficits evident to visual inspection.; however her S value was 0.623 with SN 0.528, raising suspicion of mild cognitive impairment unapparent in the images due to over smoothing. Repeat processing (3B) revealed CPi 66.0% with S 0.605 and SN 0.545, comparable to SN 0.59+0.08 for 19 patients with mild cognitive impairment. Note the visually evident parieto-occipital deficits with reprocessing (Fig 3B) consistent with amnesic, mild cognitive impairment due to traumatic brain injury.

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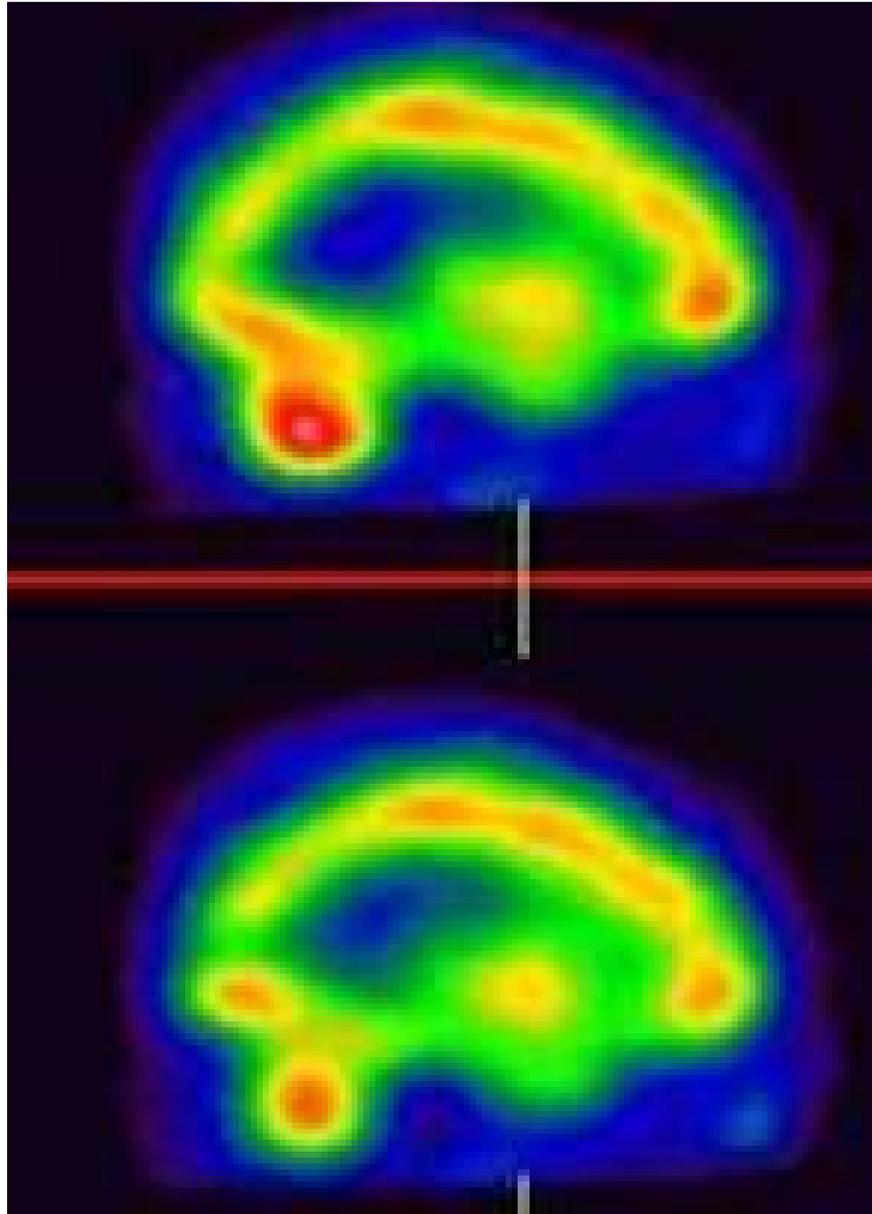


Fig 4. An 87 year-old insulin resistant woman with HbA1c 5.6% had CMi 35.0% and CPi 40% as well as late life onset of psychiatric depression (confirmed by psychiatric consultation) consistent with early Alzheimer's disease. Her SN values 1.10 for her CMi and 1.31 for the CPi analysis were toward the upper range of 10 early dementia patients with SN 0.98 ± 0.17 . Her FDG PET scan showed hypometabolism in the olfactory and parieto-occipital cortex also consistent with early dementia. Within 15 months she had frank dementia and required nursing home placement. Positive cerebral flow reserve is typical of early dementia but also occurs in early IR without dementia. The SN values in near normal patients 0.35 ± 0.05 are very different from either early dementia $p < 2.9 \text{ E-}7$ or mild cognitive impairment $p < 2.0 \text{ E-}10$.

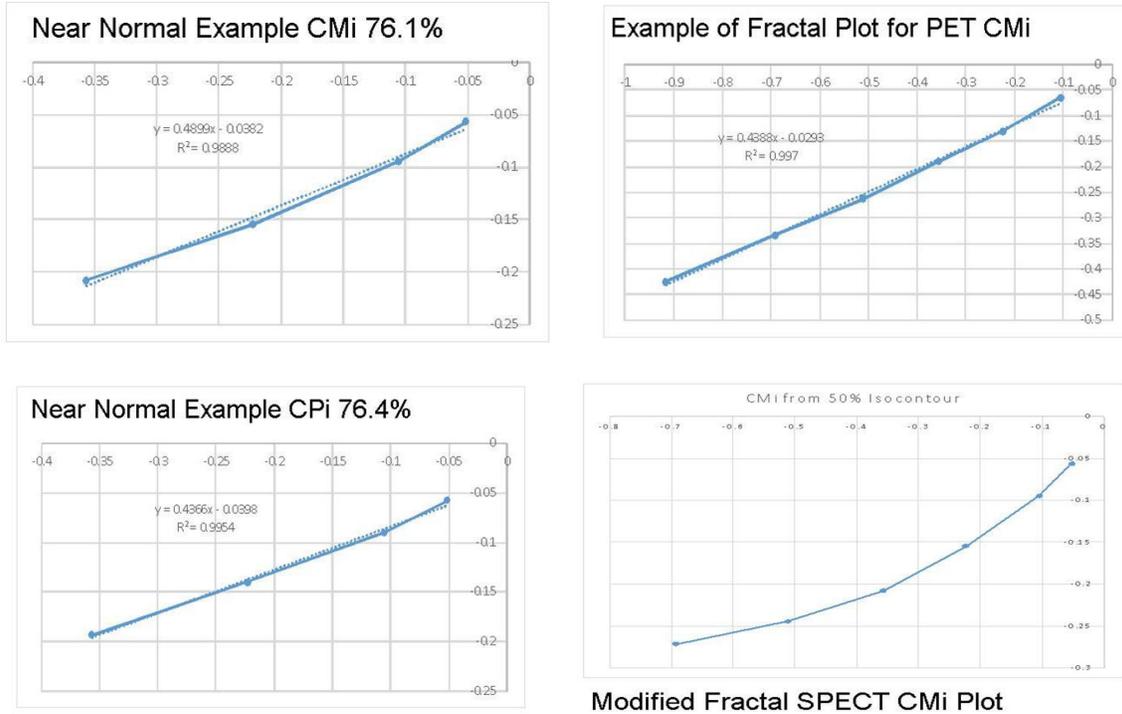
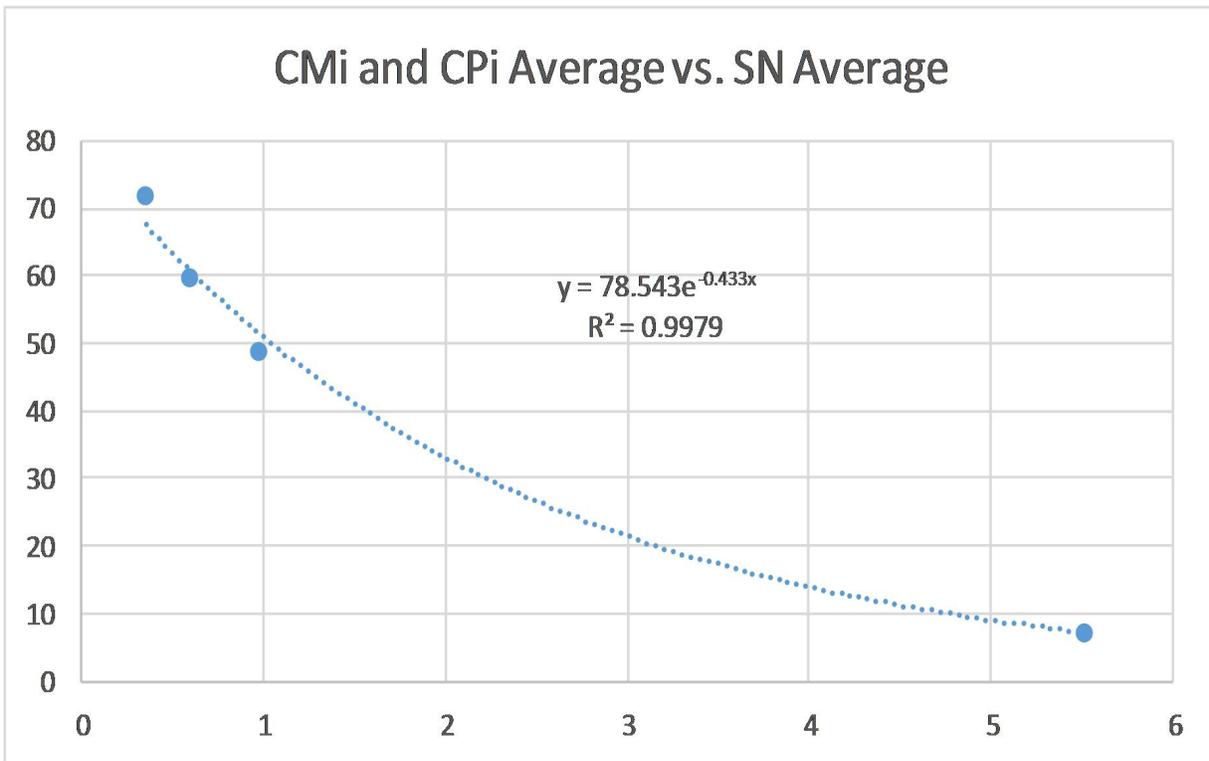


Fig 5. Examples of graphs for determining the modified fractal parameter S, the positive slope of the natural log of each average measured count (on the y axis), normalized by dividing by the peak count in the image, plotted against the natural log of the isocontour (on the x axis) which contains that average count. The theoretical limiting isocontour is 100% = 1.0 which has natural log = 0. Similarly, the average count divided by the maximal count in the image approaches a value of 1.0 and natural log of 0 as the isocontour approaches 100%. Hence, such graphs approach an intercept of (0,0) and one measure of the goodness of fit is the minimization of the calculated intercept. Note that the graph for PET data, shown above on the left, has nearly the same slope throughout the entire range which includes contours within the image, from about 50% to about 95%. The SPECT data plot on the upper right shows a curve but a limiting slope near the intercept which is nearly equal to that obtained (for the same patient and same resting state) for PET. For properly attenuation corrected SPECT data, such curves would likely be more similar to those for PET. If the data points are weighted for uncertainty, the limiting slope near the intercept is also emphasized, since, until limited by the instrument resolution and ability to define small areas, the standard error (and coefficient of variation) of the data points decreases progressively toward the (0,0) intercept. For the MiE PET with resolution near 5 mm and E.cam SPECT with resolution near 6 mm, the limiting valid isocontours are usually near 95%.

5.



Graph above shows the relation between average CMi and average SN for patients who are near normal, mildly cognitively impaired, or have early or frank dementia which follows an exponential relation. So far the highest SN observed is 5.52 for an IR patient with advanced dementia who has CMi 7.25% and scores so poorly on standard screening tests (MoCA < 5/30; TYM < 10/50) that his score is difficult to determine. Patients with CMi near zero have minimal cortical function and are often near death.

Conclusions

Advantages of the modified fractal analysis presented include:

High sensitivity detects abnormalities often not visually apparent in images.

Most statistically robust parameter known for MCI vs. normal or dementia.

Standard isocontour software available with nearly all manufacturers.

Intuitively simple: higher slope indicates more heterogeneous, more abnormal image.

Excellent reproducibility with PET or SPECT.

High precision permits therapy decisions regarding disease progression.