

The Product of Normalized Cerebral Metabolic and Cerebral Flow Reserve Factors Accounts for most Variability in Mild Cognitive Impairment and Early Dementia

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Abstract #32474

The Product of Normalized Cerebral Metabolic and Cerebral Flow Reserve Factors Accounts for most Variability in Mild Cognitive Impairment and Early Dementia

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Background: Cognitive impairment includes neurodegenerative and cerebrovascular components which are seldom isolated and usually coexist. Neurodegeneration is primarily characterized by metabolic markers such as fluorodeoxy-glucose (FDG). We reported direct relation between cerebrovascular disease, including stroke, and a brain SPECT derived cerebral flow reserve index (FRi). Here we report that the product of a scaled, normalized cerebral metabolic index (CMi) and FRi, both from brain SPECT, quantitatively measures cognitive impairment.

Methods: Tc-99m-HMPAO or Tc-99m-ECD were injected in quiet, dark rooms for basal (CMi) or post perfusion stimulants (e.g. 0.8 mg sl nitroglycerin or 500 mg IV acetazolamide) for the cerebral perfusion index (CPi) and $FRi = CPi - CMi$. Both CMi and FRi were normalized by subtracting them from their average peak value or range. Cognitive function was monitored by Test Your Memory (TYM). Interrelated risk groups for cognitive impairment included patients with traumatic brain injury (TBI), hypertension (BP >140/90), insulin resistance (IR), diabetes mellitus (DM), thyroid disease (Td), pituitary disease (Pd), high or low glomerular filtration rate (GFR in ml/min), monitored by deviation from $GFR = 160 - A$, where A is age in years and GFR estimated from serum creatinine or cystatin C.

Results: Near normal patients (n = 52), age (51.0+-14) years, similar to other patients, had FRi (9.7+-3.2), CMi (56.4+-9.9) and TYM (47.0+-1.8). Average DTYM = 50 - TYM correlated (r = 0.935; p = 0.001) with the normalized product $NP = (0.1)(70 - CMi)(20 - FRi)$ so that $DTYM = (0.20)(NP) + 0.17$. For near normal patients, DTYM 3.0, NP 13.9; for 52 Pd, DTYM 9.8, NP 46.5; for 100 high GFR, DTYM 7.5, NP 35.2; for 173 DM, DTYM 5.9, NP 31.9; for 51 IR, DTYM 7.3, NP 31.2; for 125 hypertensives, DTYM 6.3, NP 35.5; for 91 TBI, DTYM 6.3, NP 32.3; and for 57 Td, DTYM 7.6, NP 32.7. FRi = 0 corresponded to 14% adult incidence of stroke and 83 patients with stroke or TIA had $FRi = -0.4 \pm 8.8$

Conclusion: The normalized product of FRi, the cerebral flow reserve index, and CMi, the cerebral metabolic index is a practical, quantitative measure of mild cognitive impairment and early dementia.

1.

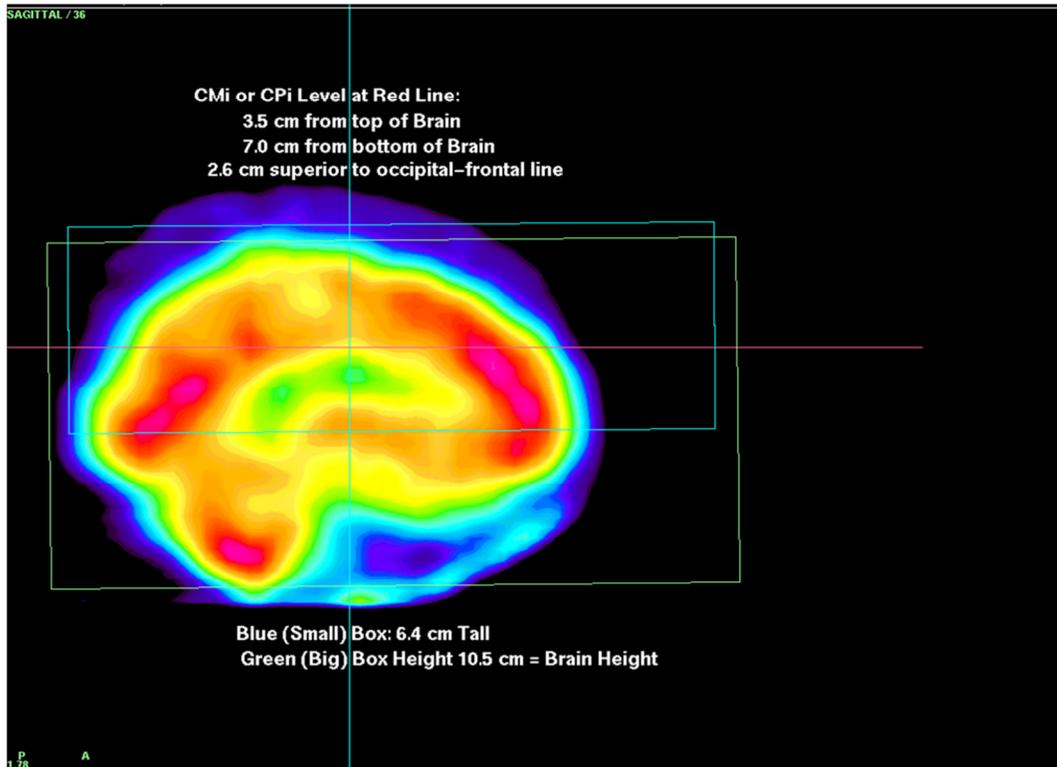


Fig. 1: Axial SPECT slices are parallel to the brain long axis from occipital to prefrontal. For the Cortical Metabolic index (CMI), one or more axial slices are centered one third of the way from the top of the brain, just superior to the roof of normal-sized lateral ventricles. Activity display is a Sokoloff color scale, with white for peak brain, black for zero and spectral colors for intermediate activities. Isocontour enclosed areas contain activity > a % of peak activity. In an axial slice, a 30% isocontour represents total brain activity and a 60% isocontour represents cortical activity.

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Fig. 2: Below are Brain SPECT images for a 66 year-old man whose scan strongly resembles Alzheimer's disease, illustrating:

A) The neurodegenerative component contributing to impaired cognition.

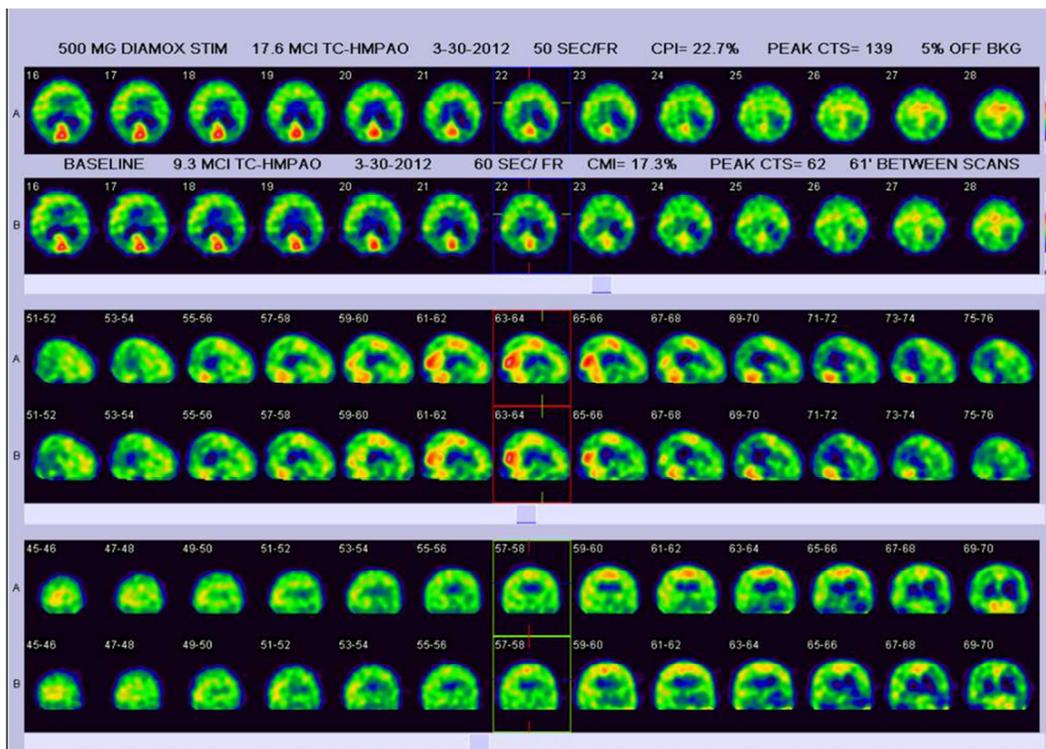
B) Normalization to cerebellum instead of peak brain uptake when the patient opens his eyes during tracer uptake and causes high occipital activity (this happens frequently with Tc-99m-ECD even if the patient's eyes are closed).

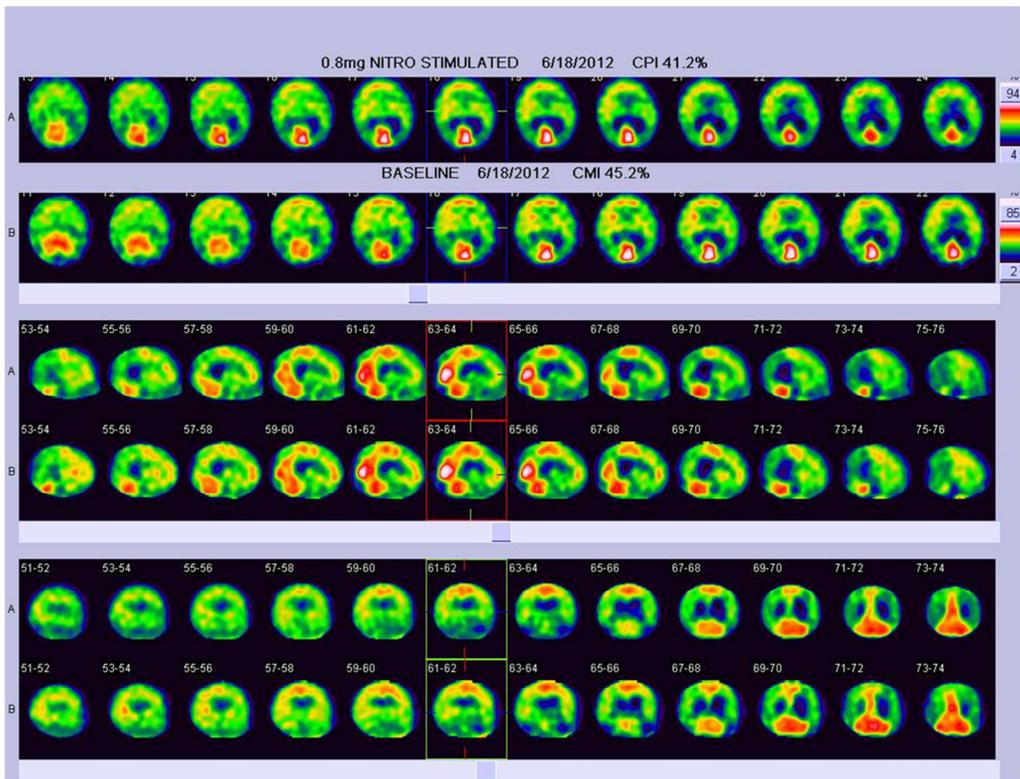
C) Interval improvement from the first (top) to second (bottom) scan, not typical of Alzheimer's disease but more typical of neurotoxic chemical exposure: the patient worked as a dentist for many years and had abnormal fractionated urine porphyrins consistent with mercury exposure.

D) The Cortical Metabolic index (CMi), the ratio of activity within the 60% isocontour to that within the 30% isocontour, a measure of cortical brain function.

E) The Cortical Perfusion index (CPI), 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.

F) The difference between CPI and CMi is a measure of cerebral flow reserve (FRi).





3.

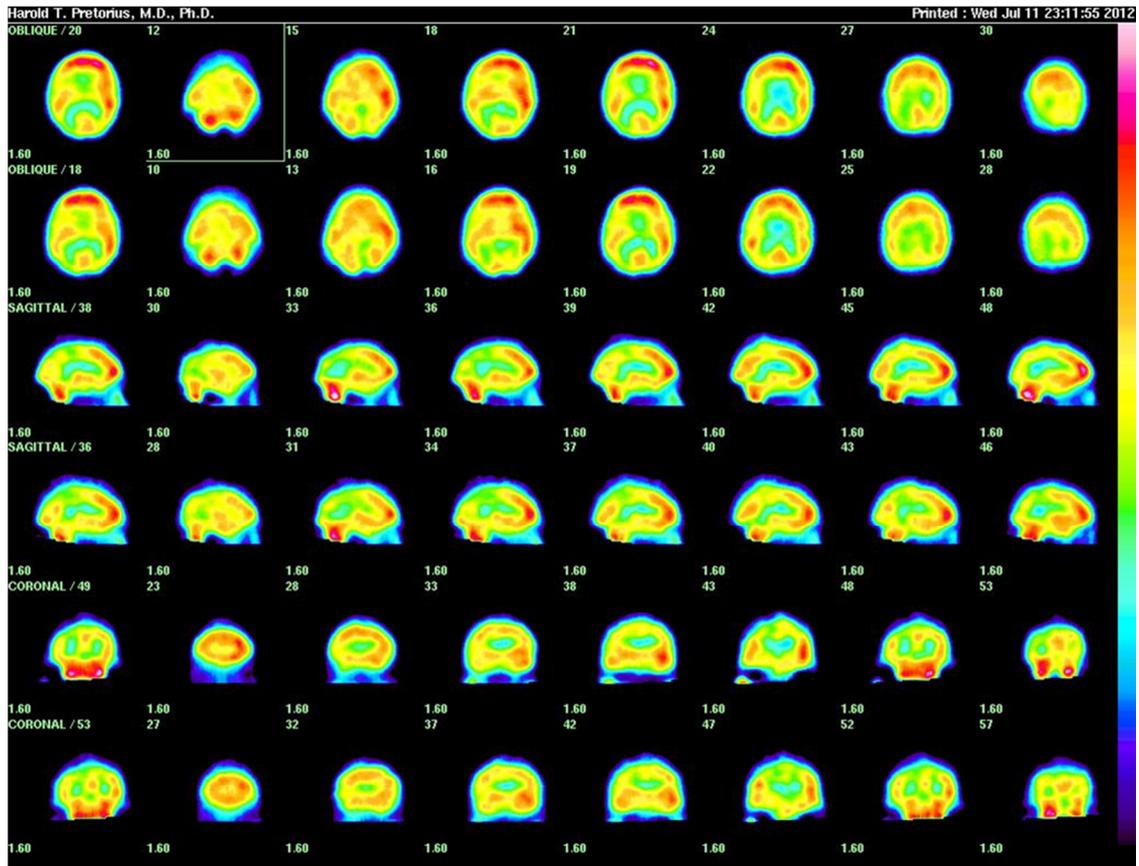
Cognitive Impairment Risk Groups	Number of Patients
Low Disease Likelihood Patients: Mean Age: (53.1+/-15.7) years Cerebral Flow Reserve index Mean (CFi) = CPi - CMi = (10.91+/-3.20)% Mean TYM = (47.9+/-0.9)% Mean CMi = (57.3+/-4.6)%	33
Untreated Pituitary Patients (PitD) Age (54.2+/-15.0) Mean CFi = (-6.0+/-5.8)% Mean TYM = (43.5+/-3.5)% Mean CMi = (56.8+/-8.0)%	61
Treated Pituitary Patients Age (47.5+/-14.3) Mean CFi = (5.9+/-7.0)% Mean TYM = (46.3+/-2.04)% Mean CMi = (50.3+/-7.1)%	55
Hyperfiltration (High GFR) Age (48.10+/-13.84) Mean CFi = (-2.3+/-7.0)% Mean TYM = (43.3+/-3.9)% Mean CMi = (55.6+/-6.6)%	56
Renal Disease (RD) Age (63.0+/-10.0) Mean CFi = (-0.18+/-7.1)% Mean TYM = (41.3+/-4.3)% Mean CMi = (52.59+/-7.34)% (GFR < 60 ml/min; Cystatin C > 0.85 mg/L)	70
Hypertensive (BP) Age (55.07+/-13.23) Mean CFi = (0.25+/- 9.3)% Mean TYM = (43.7+/- 3.8)% Mean CMi = (52.2+/- 8.0)%	122
Traumatic Brain Injury (TBI) Age (51.57+/-7.12) Mean CFi = (0.42+/-6.4)% Mean TYM = (42.4+/-4.0)% Mean CMi = (53.1+/-7.1)%	102
Diabetes mellitus including RD Age (56.3 +/-12.28) Mean CFi = (-0.02+/-9.2)% Mean TYM = (43.6+/-5.6)% Mean CMi = (54.0+/-6.7)%	163
Insulin Resistant Nondiabetics Age (55.02+/-12.35) Mean CFi = (-1.7+/-7.5)% Mean TYM = (43.3+/-3.6)% Mean CMi = (52.1+/-7.8)%	67
Stroke Age (55.59+/-10.21) Mean CFi = (-2.4+/-7.3) Mean TYM = (41.3+/-4.5)% Mean CMi = (53.1+/-7.6)%	62

4.

Fig. 4: Tc-99m SPECT for a 75 year-old diabetic man with a right hemispheric stroke, illustrating::

A) The vascular component contribution to impaired cognition. with abnormal decreased FRi – 6.6% vs. normal + (10.9+3.2)%.

B) TYM 41 for this patient is below the initial cutoff of 42 but above the revised cutoff of 30 which has reported sensitivity 0.73 and specificity 0.88 to identify dementia.



5.

Fig. 5: Graph of data from panel 3 showing correlation of normalized cognitive function (50-TYM) vs. the cross product of normalized cortical metabolic index (CMi) and normalized flow reserve index (FRi). Patients with > 30% background contribution of CMi to CPi were excluded.

FRi correlates strongly with the cerebral flow reserve ratio, FRr, which is the ratio of stimulated to basal activity per unit dose of tracer injected. The advantage of FRi vs FRr is a broader range and greater sensitivity, while FRr has the advantage of being better known and having less statistical variance.

Renal corrections for this plot were as previously reported, using corrected FRi = $FRi - (K)(1-L)(1-L)$ with $L = GFR/(160-A)$ and $A = \text{age in years}$ and $K = 5.00$, approx. half $K = 10.25$ which relates FRi to % Stroke incidence.

