

Stimulated-Perfusion-Metabolic Stress Brain SPECT

Harold T. Pretorius, MD, PhD, Christopher Kircher, MD, Lauren E. Holtman, RN, Nichole M. Richards, CNMT, Luis F. Pagani, M.D., Jurgen Horst, MD

Abstract

Stimulated perfusion and basal metabolic SPECT or PET are the current state of the art for neuroimaging diagnosis of dementia, particularly Alzheimer's or mixed vascular dementia. A logical next step is to develop a metabolic stress protocol to more sensitively reveal early dementia. Since compromised central cholinergic transmission is a key feature of Alzheimer's and other dementias, we are developing anti-cholinergic pharmacologic stress protocols using SPECT tracers of brain metabolism, Tc-99m-ECD or FDG. The contribution of vascular disease is monitored by perfusion-stimulated brain SPECT using the perfusion tracer Tc-99m-HMPAO after a stimulant such as acetazolamide. Metabolic stress SPECT promises reliable dementia diagnosis at an early stage of pre-dementia, an ideal point to initiate pharmacologic studies of dementia therapy.

Correlative ICAD Abstract

Title: Brain basal metabolism and flow reserve predict therapeutic response in most cognitively impaired patients

Category: Diagnosis and Disease Progression Neuroimaging

Author(s): Harold T. Pretorius¹, Chris Kircher², Lauren E. Holtman³, Nichole M. Richards², Luis F. Pagani², ¹The Christ Hospital, Cincinnati, OH, USA; ²The Cincinnati Cognitive Collaborative, Cincinnati, OH, USA; ³Cincinnati Cognitive Collaborative, Cincinnati, OH, USA. Contact e-mail: htpretorius@msn.com

Background:

Patterns of basal brain metabolism and flow reserve, determined by comparing basal and stimulated perfusion, are widely described to correlate with various causes of cognitive impairment; however, there are few descriptions correlating these patterns with patient's therapeutic responses.

Methods:

SPECT scanning used a dual-head gamma camera with 5.5 mm resolution. Patients received 20 mCi Tc-99m-HMPAO for stimulated or basal perfusion (also a surrogate for basal metabolism) or 10 mCi F-18-FDG or 20 mCi Tc-99m-ECD for basal metabolism, injected in a quiet, dark room. Perfusion stimulants were acetazolamide 500 mg IV, nitroglycerin 0.6+/-0.2 mg sublingual, omega 3 unsaturated acid ethyl esters (Lovaza^R) 10 gram oral, or Mona Vie^R (acai fruit juice) 100 ml oral. Cerebral Perfusion and Metabolic indices (CMi, CPi) for each patient, including 20 with low likelihood of disease, were calculated from the SPECT images. Patients were studied in the course of neurologic and neuroendocrine practice after complaints of cognitive impairment. Therapies included acetyl-cholinesterase inhibitors, Namenda^R, Lovaza^R, nonbranded fish oils, antihypertensives, statins and amantadine (for traumatic brain injury).

Results:

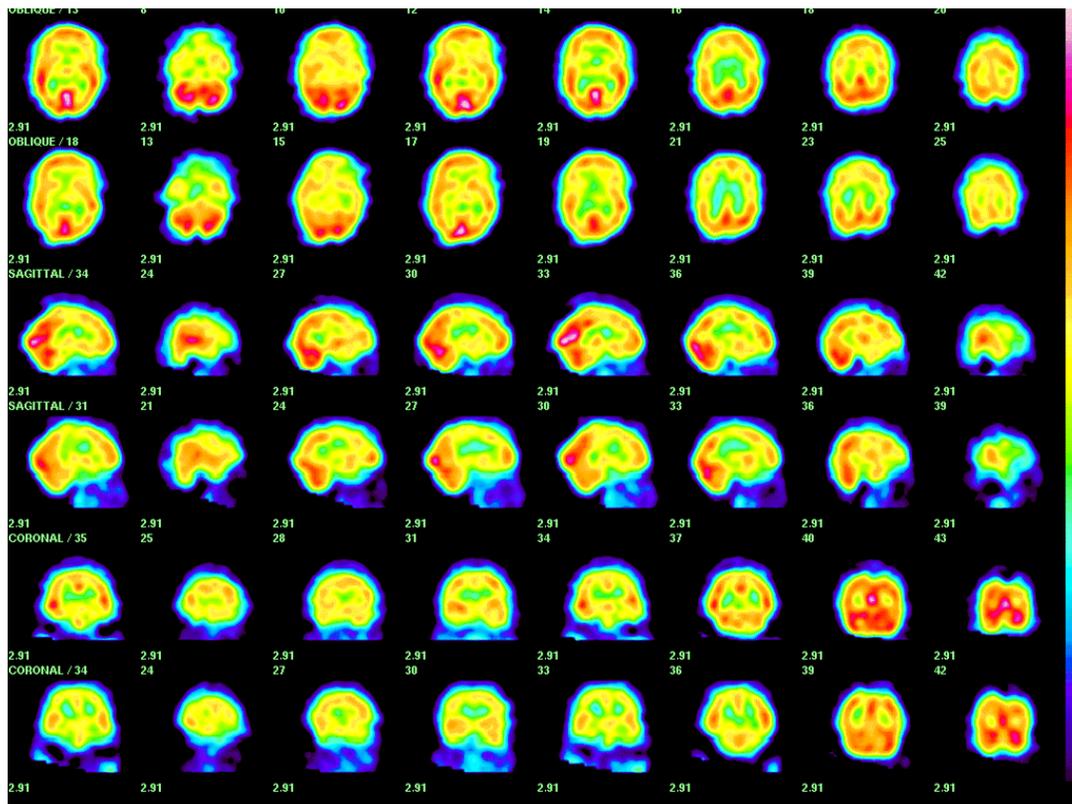
Brain SPECT defined three patterns: 1) $CMI + (5 \pm 2)\% = CPI$ (normal if $49\% < CMI < 71\%$) ; 2) $CMI + (5 \pm 2)\% < CPI$; 3) $CMI + (5 \pm 2)\% > CPI$. Therapeutic responses in 6 to 18 months among 20 \pm 5 patients in each group were best (60% improved) for group 3, intermediate (30% improved) for group 2 and worst (< 10% improved) for group 1. Diagnoses included multiple causes of mild cognitive impairment in 80% and dementia in 20%. Over 70% of dementias were mixed, predominant types: vascular in 40%, Alzheimer's in 30%, probable Lewy body in 15%, fronto-temporal in 5%, traumatic brain injury in 5% and miscellaneous in 5%.

Conclusions:

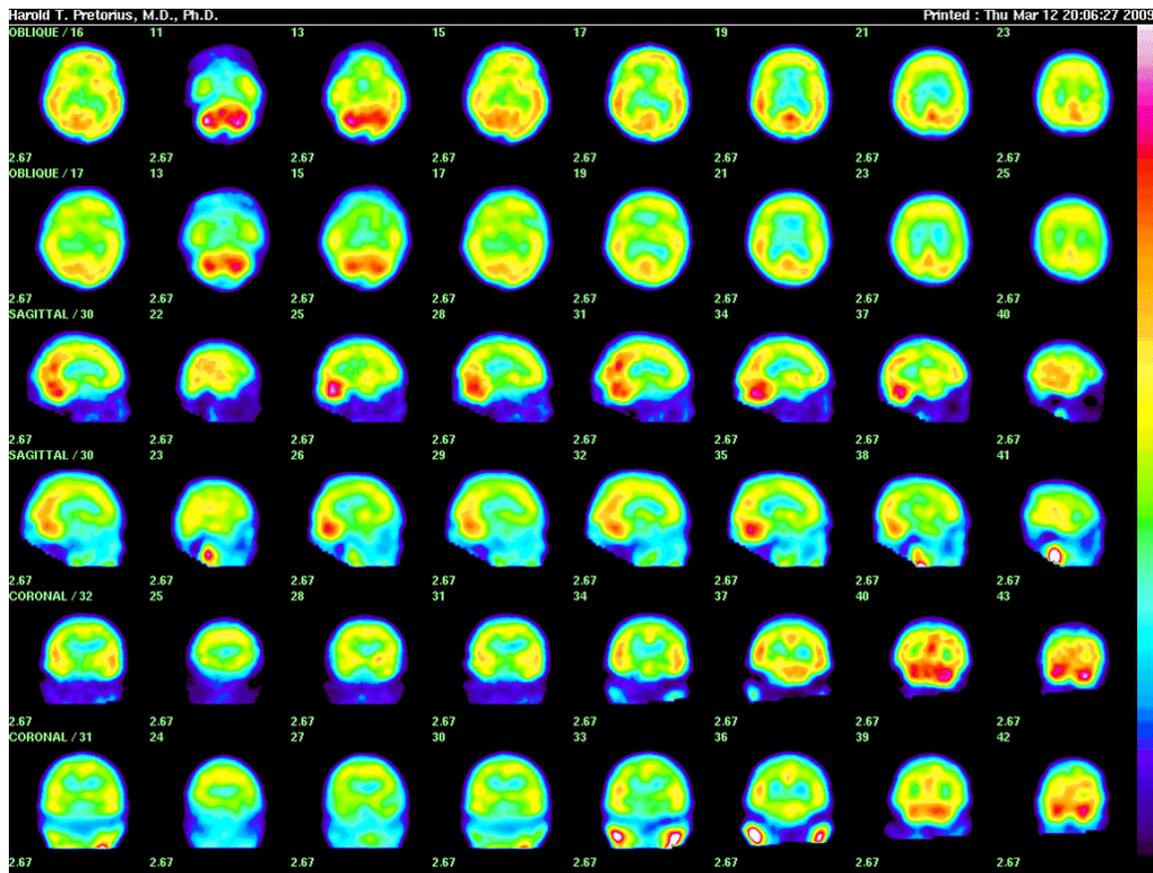
Stimulated perfusion is normally slightly increased over basal metabolism as defined by brain SPECT. Patients with decreased cerebral flow reserve (perfusion deficits) respond more readily to widely available therapy than those with predominant metabolic deficits and more intact flow reserve which characterize early neurodegenerative diseases. Patients with similar, fixed deficits in perfusion and metabolism (nonresponsive to perfusion stimulants) include advanced neurodegenerative and vascular dementias which have the worst prognosis.

1

Basal (bottom of each set of three images) and IV acetazolamide-stimulated (top of each set of three images) brain SPECT: 54 year-old type 2 (noninsulin dependent) diabetic woman, well-controlled hypertensive on angiotensin converting enzyme inhibitor, fosinopril, treated for depression with sertraline. Tracer distribution is normal, apart from minor left orbitofrontal deficit (sagittal image 33) and borderline low cerebrovascular flow reserve: Cortical Metabolic index 62.9% and Cortical Perfusion index 62.3%.

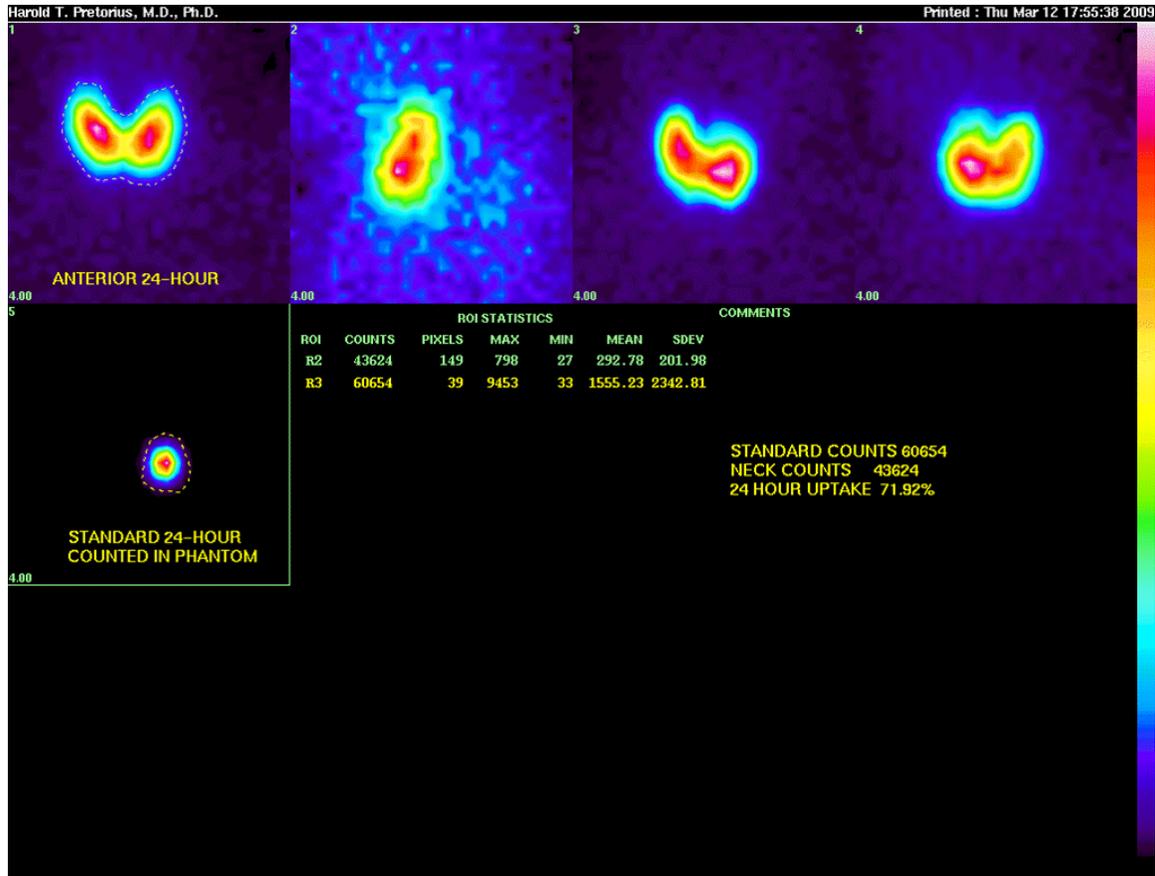


Two-day metabolic stress protocol avoiding any interference of perfusion-stimulated and metabolic stress images. Prominent salivary activity, likely due to Sjogren's, more prominent mesial temporal and subtle posterior cingulate abnormality in the metabolic stress images (lower of each paired set of three rows), despite absence of any prominent parieto-occipital abnormality. This is consistent with entorhinal and posterior cingulate (usual peak cortical) abnormality as among the earliest structural and metabolic targets of Alzheimer's pathophysiology.

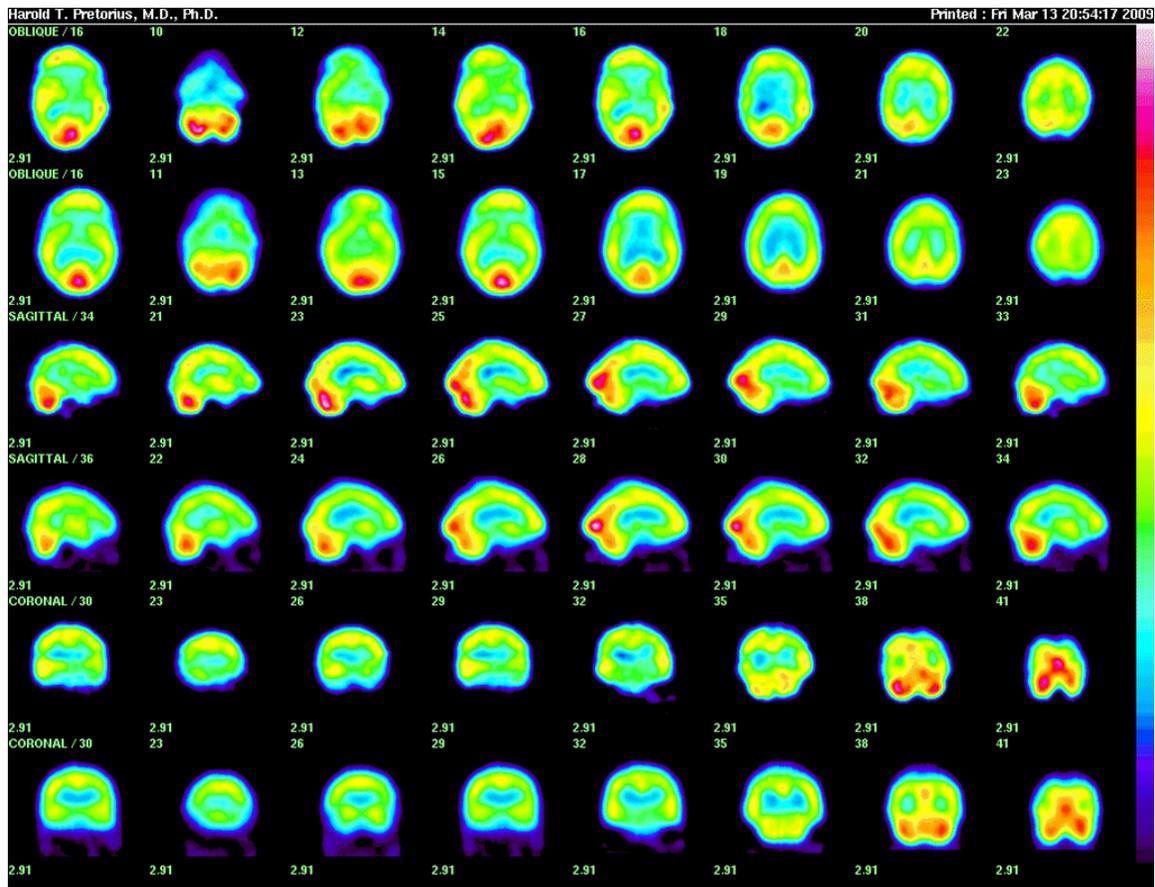


3

Thyroid scan in a 46 year-old woman with Graves' disease whose metabolic stress Brain SPECT follows. Hyperthyroid and hypothyroid patients have abnormal brain perfusion and metabolism which mimics the pattern of Alzheimer's disease with bilateral parieto-occipital and mesial temporal deficits, usually more prominent in the parametric metabolic than the parametric perfusion images. Even mild hyperthyroidism increases Alzheimer's risk 350% in longitudinal studies, indicating an area of opportunity to study pharmacologic prevention of cognitive decline.

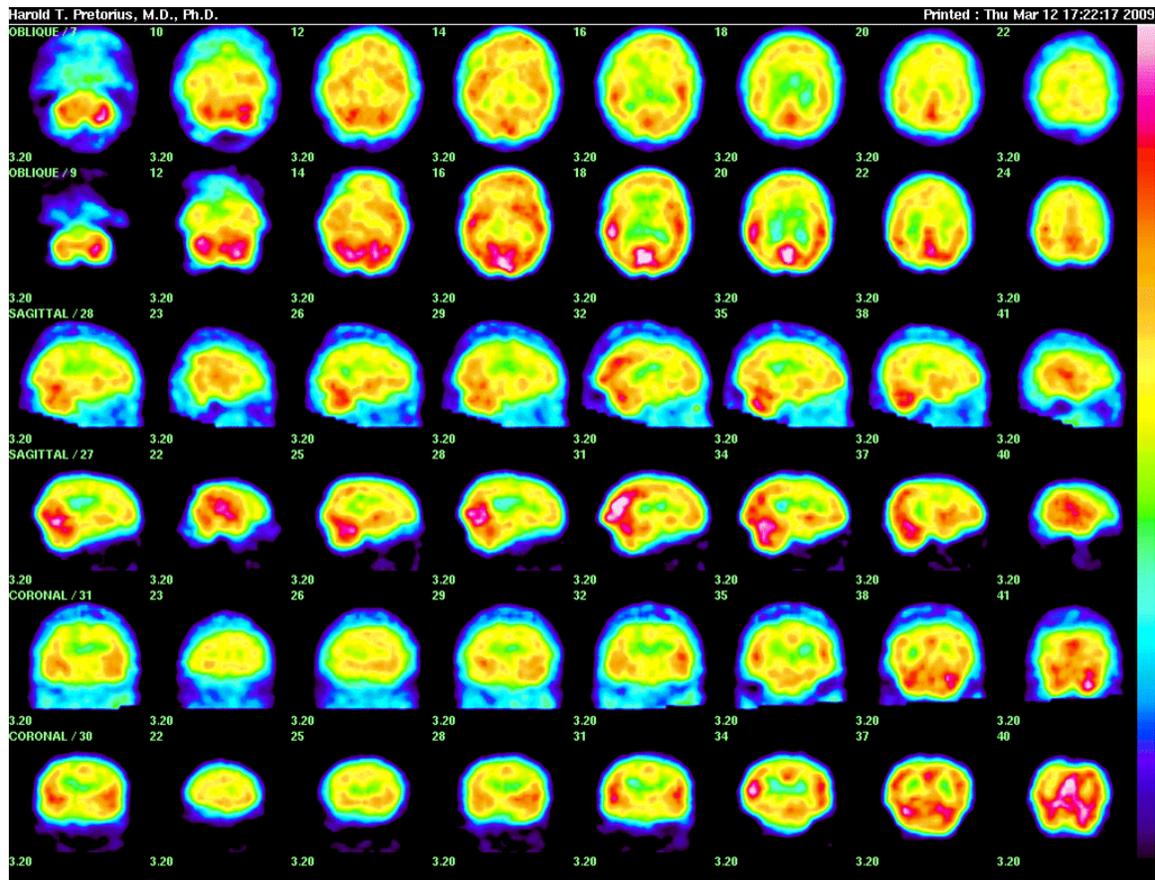


Same 46 year-old African American hyperthyroid woman whose abnormal thyroid scan is shown above, and whose metabolic stress images (upper of each set of 3 image pairs on the right) reveal a pseudoAlzheimer's pattern of decreased parieto-occipital, mesial temporal and periventricular hypometabolism more prominently than the same-day basal metabolic (lower) images. The pseudoAlzheimer's pattern is subtle in most mildly hyperthyroid patients, but may be more pronounced, as illustrated here, with severe hyperthyroidism, Tc-99m-ECD SPECT (note occipital prominence) and the metabolic stress protocol, using four transdermal scopolamine patches for four hours in this case.

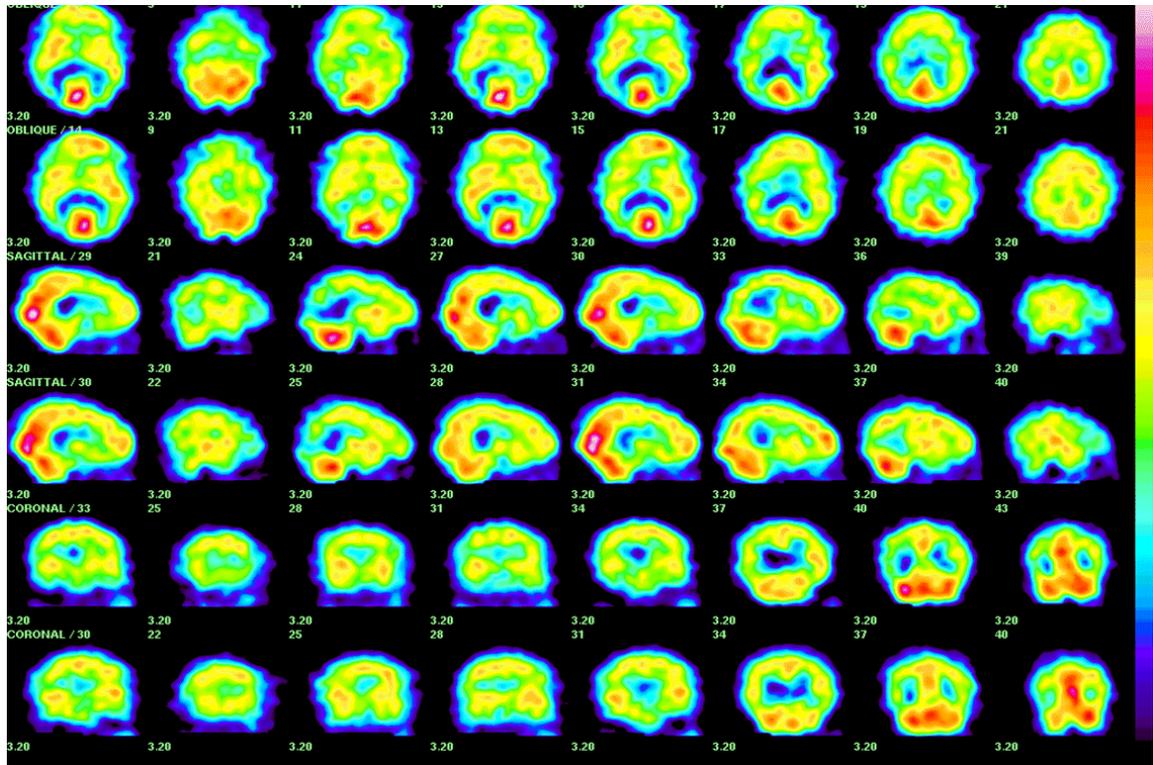
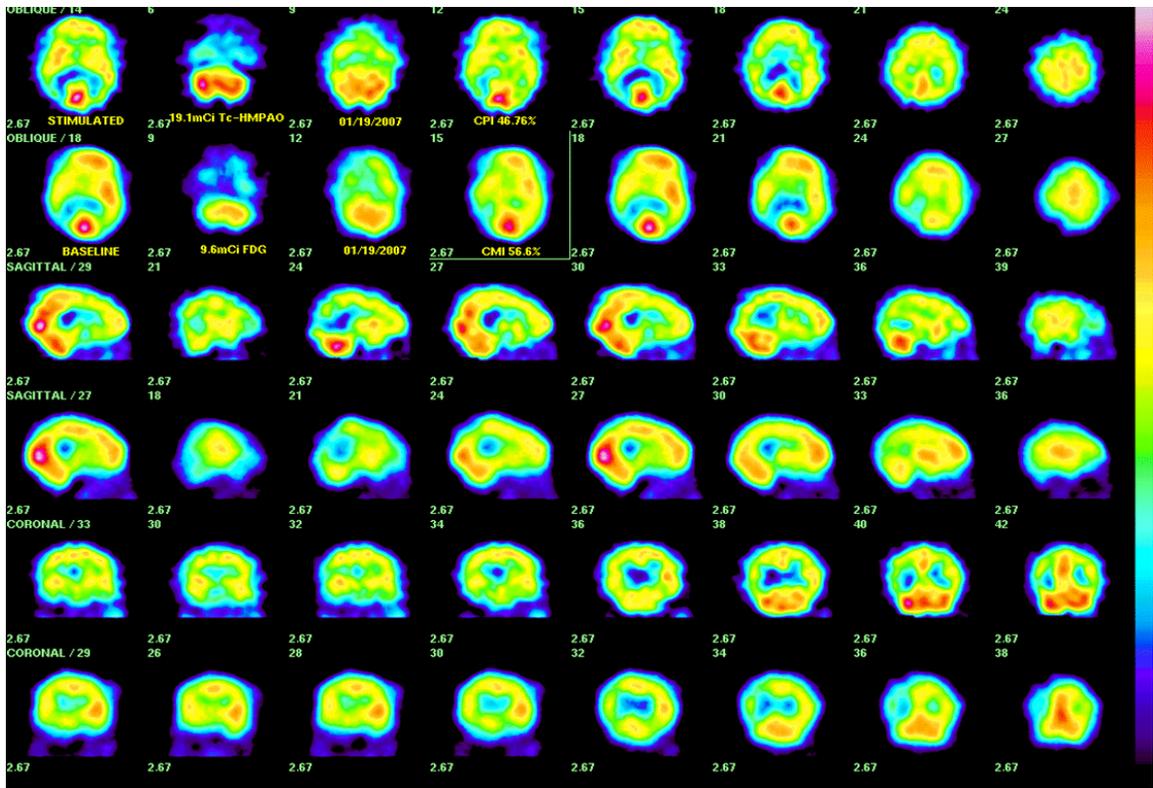


4

44 year-old woman with thyroid cancer and treated hypothyroidism, post acute depression-related opiate and nonopiate drug overdose. Metabolic stress used standard same-day protocol with post scopolamine Tc-99m-ECD (lower of each of 3 paired rows of images to the right), preceded by 1 g IV acetazolamide-stimulated perfusion SPECT (upper of each of 3 sets of images). Greater occipital activity requires cerebellar normalization. No significant interference from psychotropic drugs is identified and the study is negative for neurodegenerative disease.

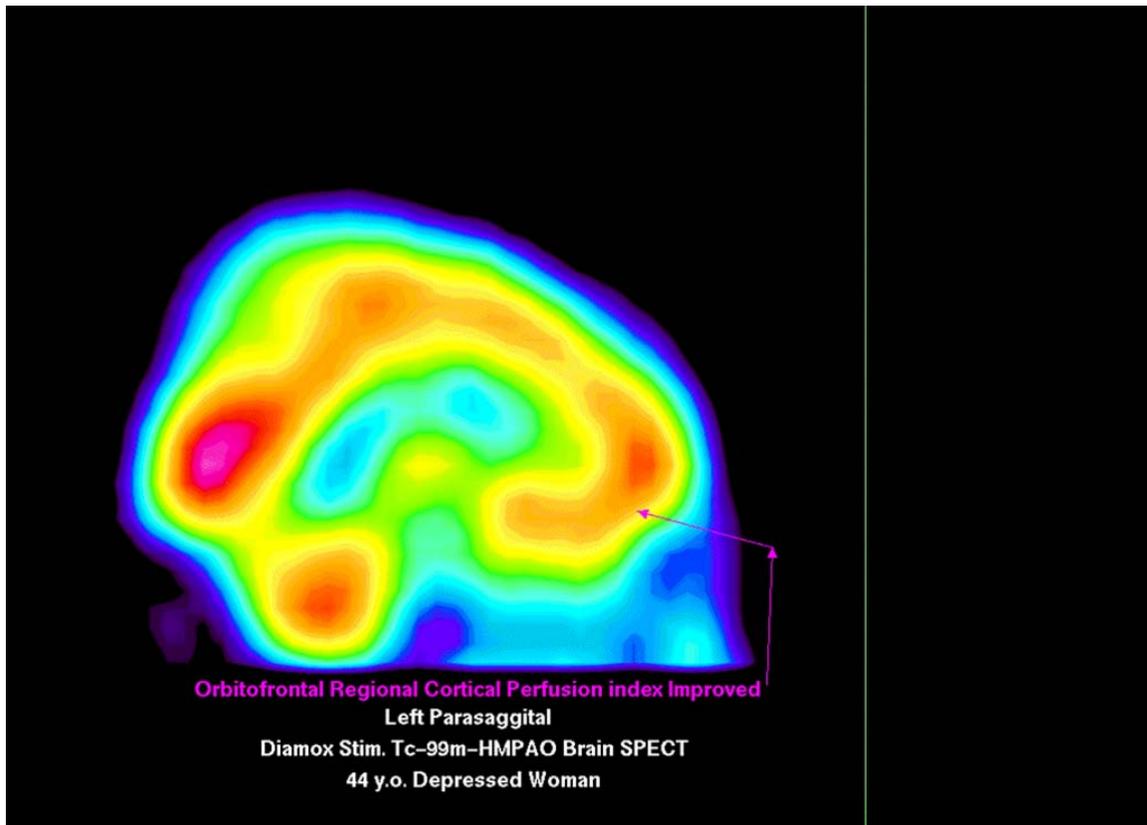


Memory loss in a 53 year-old hyperlipidemic, depressed IRS employee who had initial pattern 1: CMi 40%, CPi 35%, his Tc-99m-HMPAO basal and omega 3 unsaturated fat stimulated (stimulated top of each of 3 paired image rows to right) is consistent with mixed vascular-Alzheimer's dementia. After 6 months therapy including Aricept (later Exelon), Namenda, Lovaza, Zocor, Aggrenox (later Plavix), folic acid, Pletal, Lexapro and lithium, patient continued working with CMi improved to 50% (borderline low), CPi 46%. There was little clinical change and neuropsychological testing showed IQ 83, decreased compared to estimated premorbid IQ 120. This patient raises question of whether there is a threshold level of hypoperfusion, near 35% noted in this patient, below which available perfusion stimulants are still unlikely to result in significant improvement in either imaging parameters or clinical function. Abnormal urine porphyrins recently obtained raised the question of possible mercury exposure and potential chelation therapy with 2,3-dimercapto-1-propane sulfonic acid (DMPS).

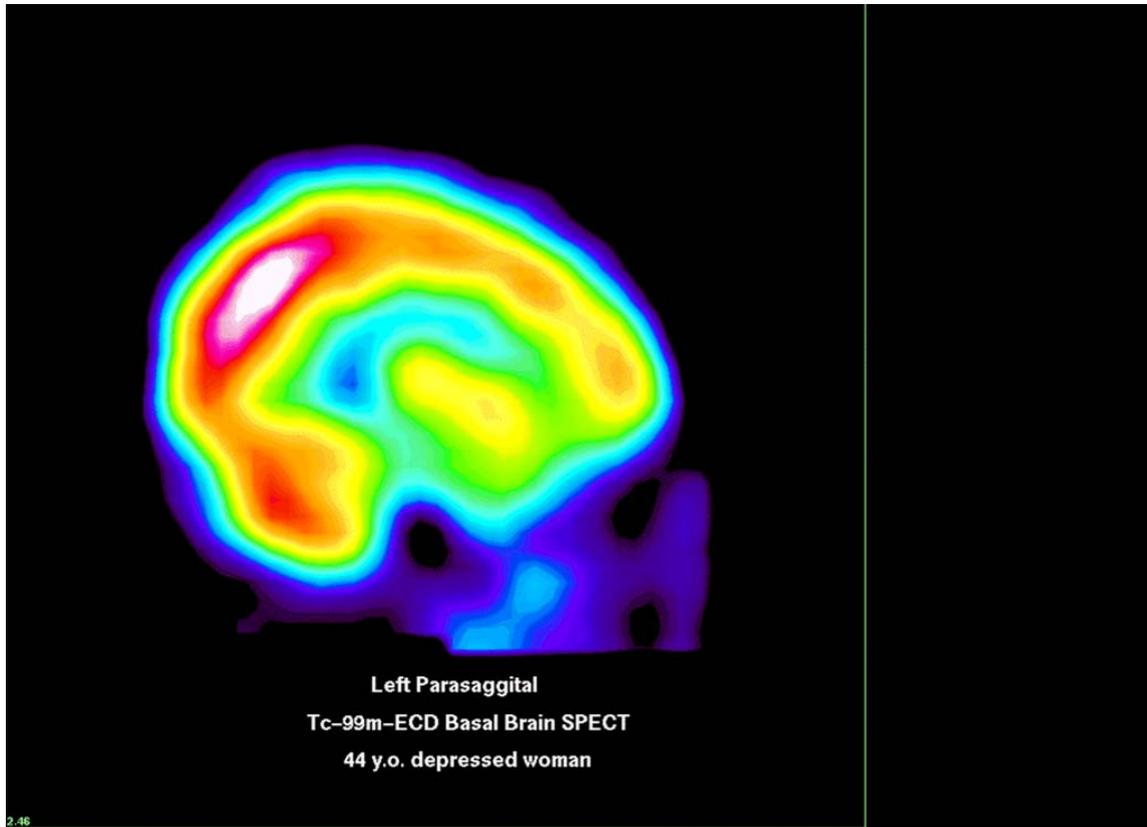


5

43 year-old depressed woman with Graves' hyperthyroidism and ophthalmopathy demonstrates regional orbitofrontal deficit in the basal study, below, and to the right, effect of perfusion stimulation with acetazolamide, which results in improvement to the extent of its near normalization. The patient complained of "brain fog", a frequent complaint in patients with Hashimoto's encephalopathy, which we and others have previously described in Graves' disease as well.

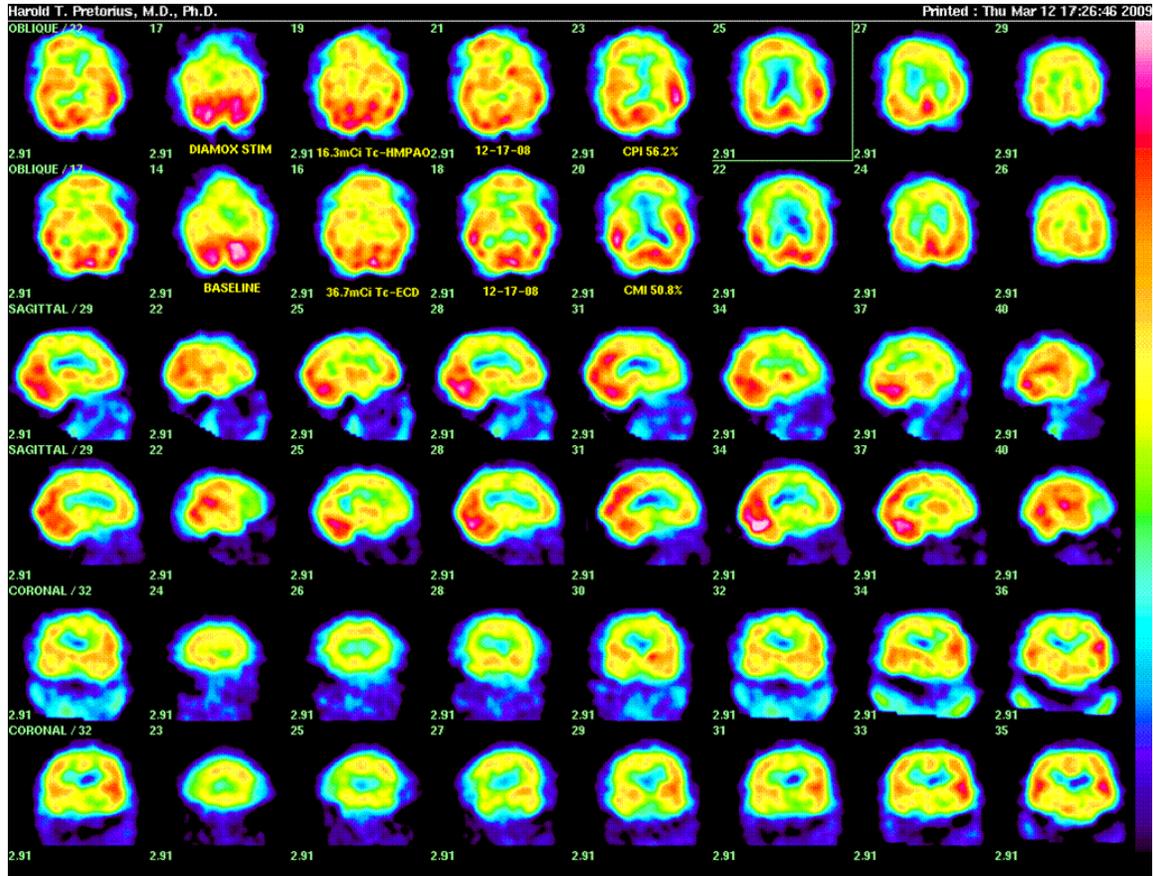


We have also described (American Association of Clinical Endocrinology National Meeting, 2008) a pseudo-Alzheimer's pattern of bilateral parieto-occipital and mesial temporal hypometabolism with preserved perfusion reserve to multiple perfusion stimulants, including the juice of the acai berry (MonaVie). This patient improved clinically with thionamide therapy and Bystolic, which may stimulate cerebral perfusion more than other beta blockers, suitable in this instance but not for migraine.

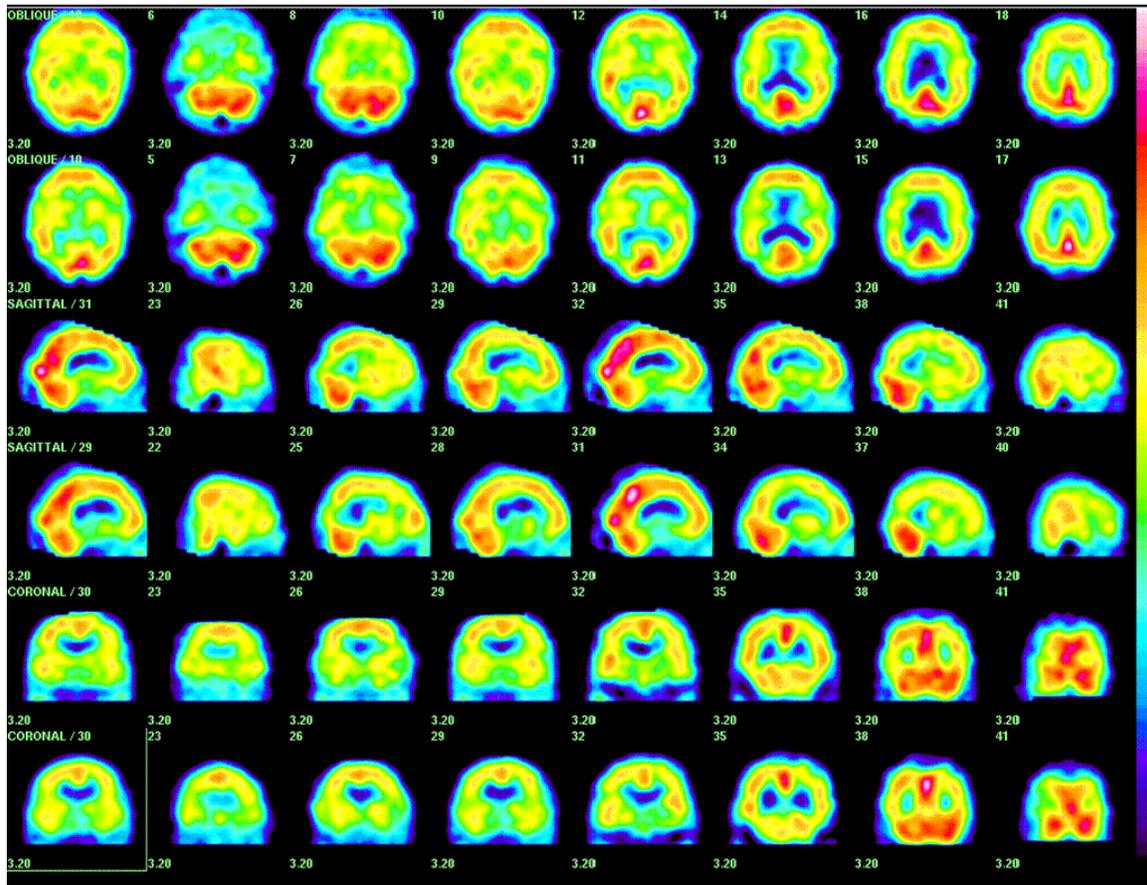


6

Insulin-resistant 64 year-old stage 1 hypertensive African American man with metabolic stress SPECT after a cortical TIA. Periventricular abnormality, consistent with leukoencephalopathy, likely related to microangiopathy is demonstrated with mild functional cerebral atrophy. The metabolic stress portion of the study is essentially negative but the perfusion-stimulation more sensitively demonstrates subtle perfusion abnormality that may precede more specific findings of Alzheimer's or mixed dementia.



Early Alzheimer's disease or Mild Cognitive Impairment (MCI) in a 70 year-old man with memory loss and CMi 49%, CPi 48% (pattern 1), the abnormalities demonstrated better by parieto-occipital and temporal regional CMi 33% and 34%. Therapy of MCI is presently approved by U.S. FDA for one natural product: Cerefolin NAC, although our experience has been principally with omega-3 unsaturated marine oil (Lovaza), renin-angiotensin-system inhibitors (eg. angiotensin converting enzyme inhibitors), cilostazol and other cerebral perfusion stimulants.



Summary

Protocols using pharmacologic stress to emphasize metabolic SPECT abnormalities can further increase the already high sensitivity of parametric metabolic brain imaging. In our experience, the comparison to pharmacologic-stimulated cerebral perfusion, as with myocardial imaging, is particularly useful to demonstrate the contribution of vascular disease, which typically compromises perfusion reserve. Patients with normal cerebral perfusion reserve, amounting to an approximately 5% increase of CPI over CMi, actually fare the worst with available therapies in our experience of over 15 years. Remarkably, those with greater deficits in CPI relative to CMi (including those with nearly equal CMi and CPI) do the best with available therapeutic agents, which arguably are primarily directed toward improvement in cerebral hypoperfusion (cf. in trials of most Alzheimer's agents the vascular or mixed dementia patients did at least as well if not better than the neurodegenerative patients). As we and others have previously reported, the frequency of mixed patterns of dementia is much greater in everyday clinical practice than classical dementia of the Alzheimer type. Further mechanisms of cerebral injury with potential for evolving therapy and metabolic stress paradigms include toxic metal exposure (eg. mercury, lead, aluminum), neurosteroid and other neuroendocrine metabolic stressors and agents modulating neurotransmitters, such as the present parenteral scopolamine pharmacologic stress protocol. One of our aims is to investigate reversal of metabolic stress as a predictor of pharmacologic responsiveness to therapy of cognitive dysfunction.