

# **Metal Toxicity Determined by Bioassay of Urine Porphyrins Correlates with Thyroid Associated Cognitive Impairment and Psychiatric Disease**

Harold T. Pretorius, MD, PhD, Mark Geier, MD, David A. Geier B.A., Ampolia Howil B.S., Nichole M. Richards, CNMT

## **Abstract**

**Introduction:** Toxic metals contribute to pathophysiology of dialysis dementia (Al), autism (Hg), neurodegeneration/neuropathy (As), Parkinson's/Lyme (Mn) and Alzheimer's disease (Al,Hg,Zn). Thyroid disease impairs cognition, likely via immunopathology after euthyroidism is achieved, and is associated with depression, especially bipolar. Urine porphyrins are associated with neuropathophysiology, perhaps via direct porphyrin toxicity. Symptomatic porphyria is rare; however, even low levels of toxic metals, particularly Hg, Pb or As, individually or in combination, often cause/s abnormal quantitative urine porphyrins whose association with thyroid disease or its related neuropsychiatry is unknown.

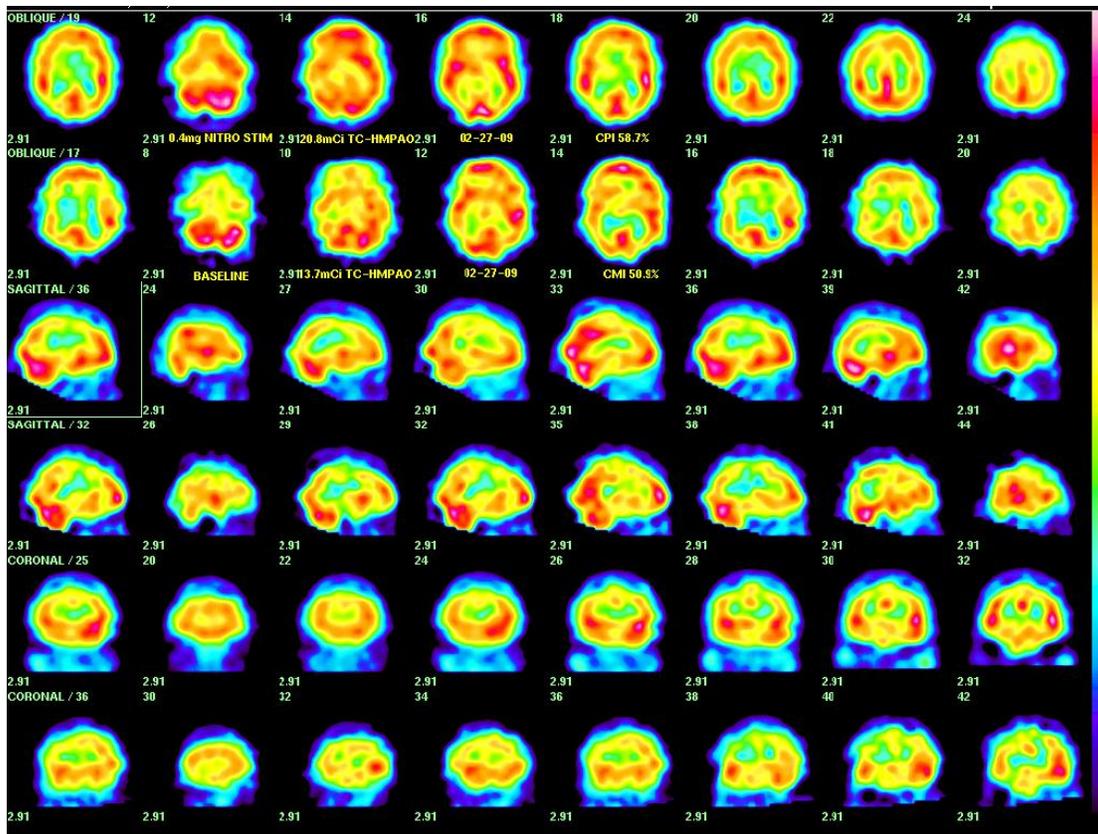
**Methods:** Urine samples were collected in dark containers, usually after achieving euthyroidism in thyroid patients. Brain SPECT used Tc-99m-HMPAO or Tc-99m-ECD IV in a quiet, dark room, to monitor cerebral pathophysiology with indices of cortical metabolism (CMi) and stimulated perfusion (CPi). Results were felt statistically significant if  $p < 0.05$  using appropriate multiple component regression or standard two parameter comparisons, including thyroid disease or its subsets vs. other neuroendocrine patients, such as diabetics and traumatic brain injured (TBI).

**Results:** Thyroid patients had significant ( $p < 0.05$ ) correlation of abnormal corproporphyrins (likely due to Hg toxicity) and CPi which was more robust than noted for diabetics. Depressed patients were nonsystematically but confidently identified and especially thyroid disease associated bipolar patients trended toward marked Hg toxicity. Patients with history of Hg and other metal or other neuropathology were more severely affected. Patients treated with dimercapto-propane sulfonate (DMPS) and agents to enhance brain perfusion, such as omega 3 fish oil or cilostazol, and immune modulators such as vitamin D, statins and antihypertensives, stabalized or improved SPECT indices and clinical symptoms.

**Conclusions:** Toxic metals, particularly Hg body burden, identified by fractionated, quantitative urine prophyrins, correlate with thyroid associated cognitive impairment and possibly neuropsychiatric disorders, particularly bipolar depression.

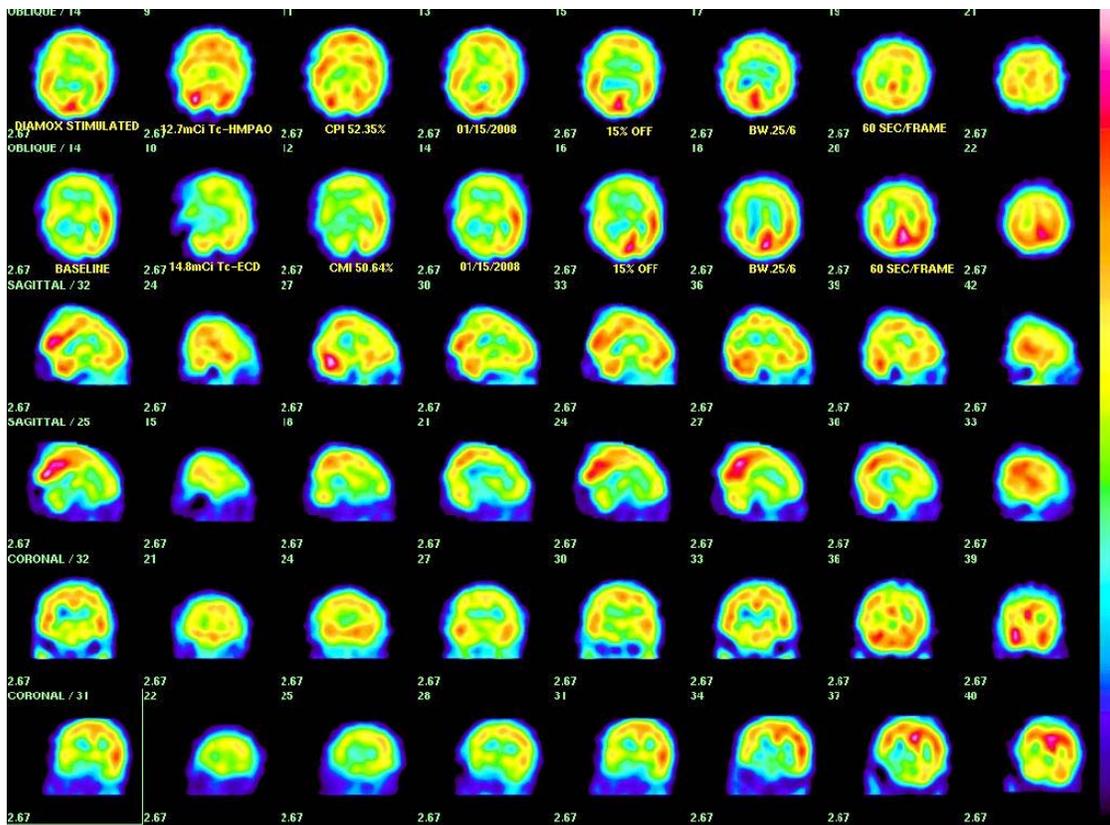
# 1.

55 year-old woman, euthyroid post I-131 therapy for Graves' disease had medical history of hypertension, 2 pack/day cigarette smoking, COPD, osteoarthritis and obesity. Her usual protocol brain SPECT (to the right) shows the perfusion-stimulated (top of each of 3 paired rows of images) with basal metabolic images on the bottom. The Cortical Metabolic index CMi 50.9% is borderline low vs. normal approx. 50-72% and Cortical Perfusion index 58.7% is within normal approx. 52-75%. Urine porphyrins were normal despite minor parietal and posterior periventricular hypoperfusion shown in the Sokoloff color scale (bar on the right) used throughout this abstract.

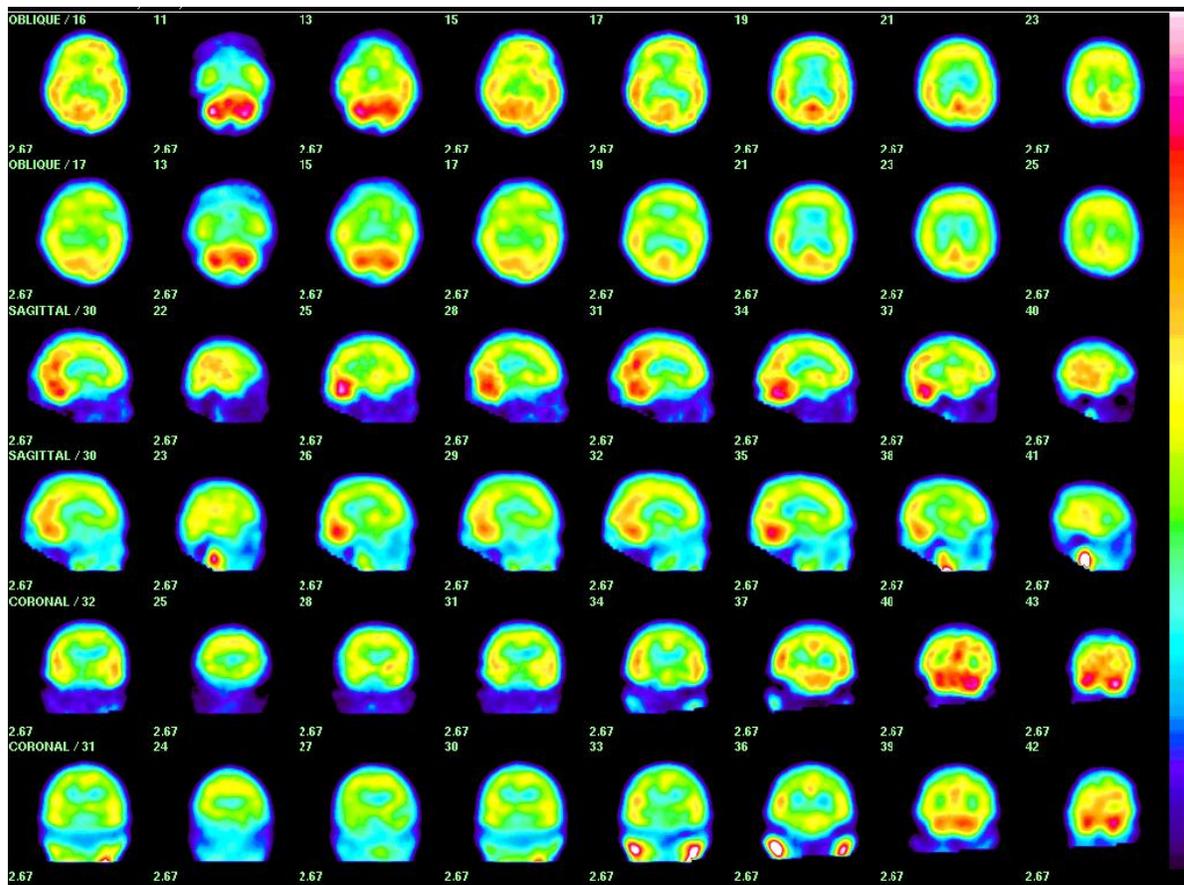


## 2.

44 year-old patient with CT confirmed mild ophthalmopathy, fatigue, tachycardia and strongly positive antithyroid antibodies consistent with Hashitoxicosis had confusion and memory loss (MMSE 26/30) consistent with Thyroid Associated Cognitive Impairment (TyAsCI). Brain SPECT using Tc-99m-ECD for the basal metabolic and Tc-99m-HMPAO for the perfusion-stimulated images shows motion artifact deficit on the right in the basal (bottom) study (correctable with meticulous processing) and a partial pseudoAlzheimer's pattern of temporal (coronal #30) and left parieto-occipital deficits in the perfusion-stimulated study.

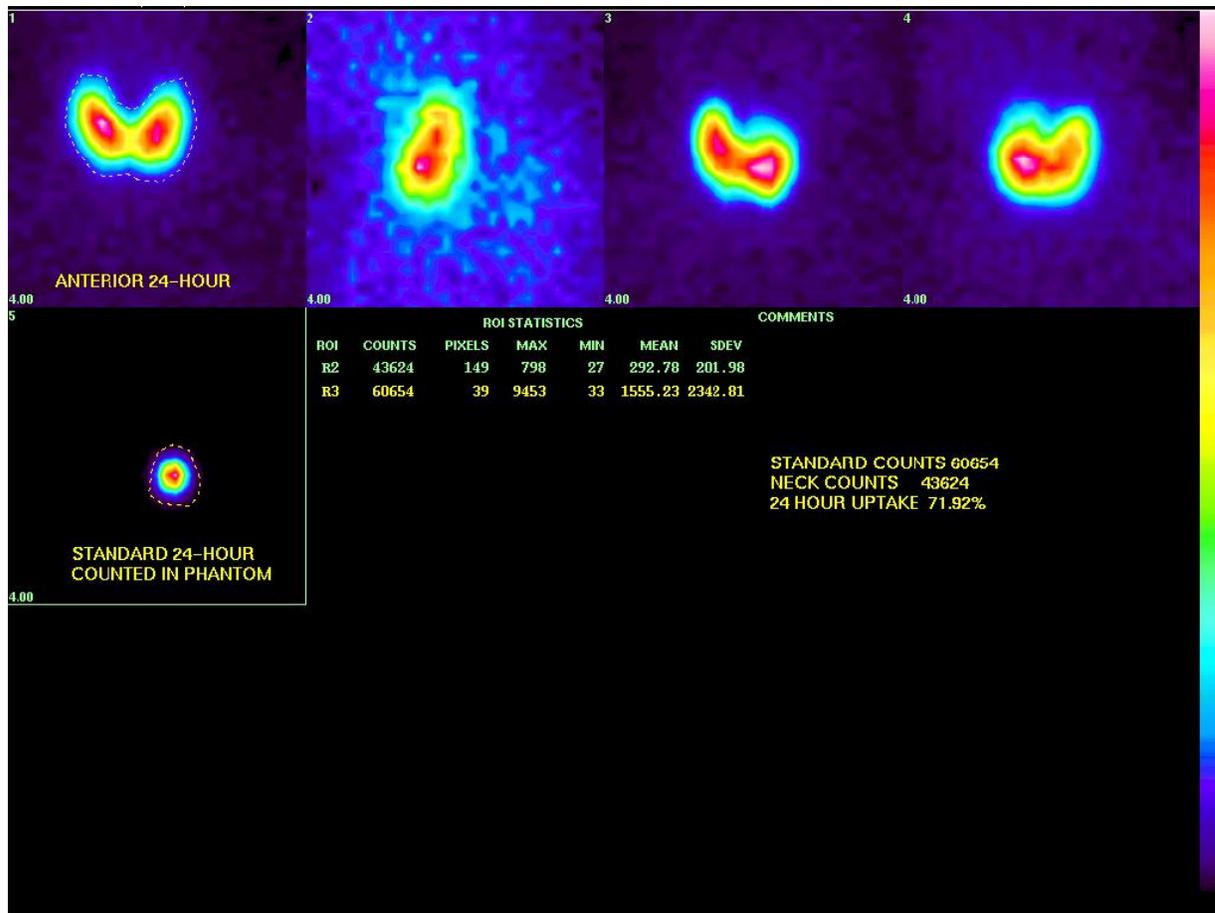


Two-day metabolic stress protocol avoiding any interference of perfusion-stimulated and metabolic stress images. Prominent salivary activity, likely due to Sjogren's, more prominent mesial temporal and subtle posterior cingulate abnormality in the metabolic stress images (lower of each paired set of 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.

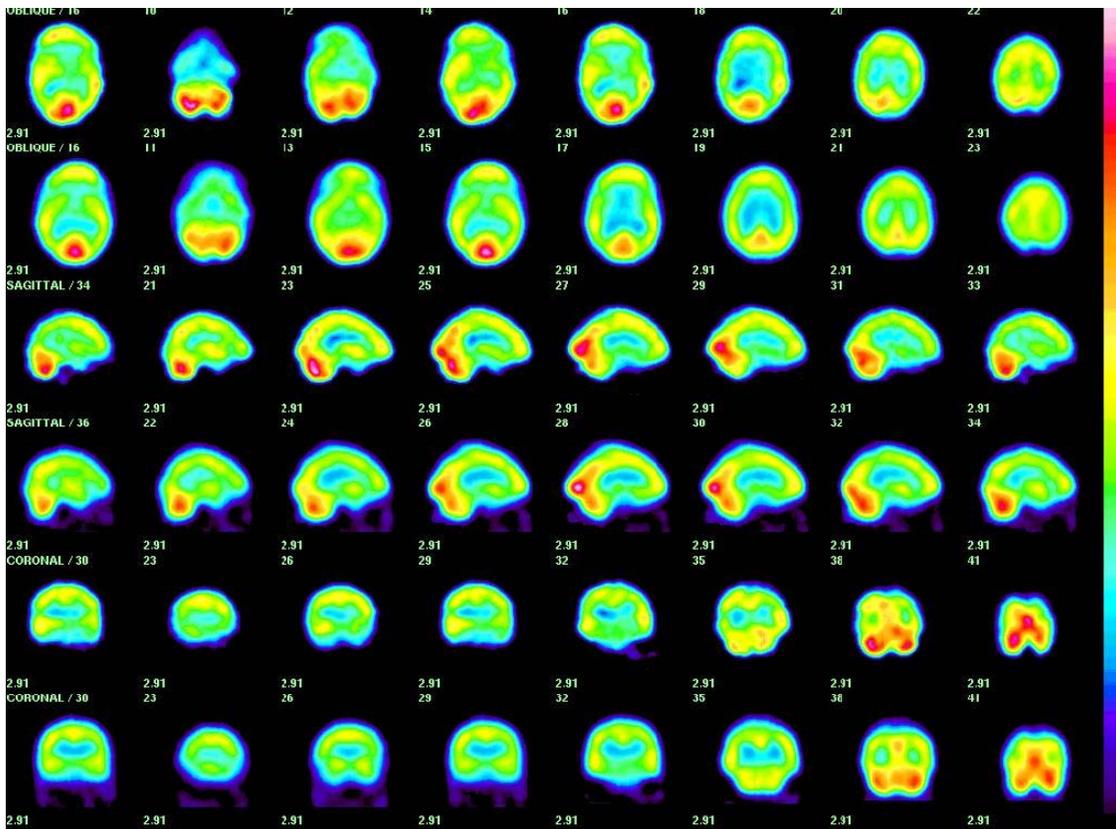


### 3.

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.

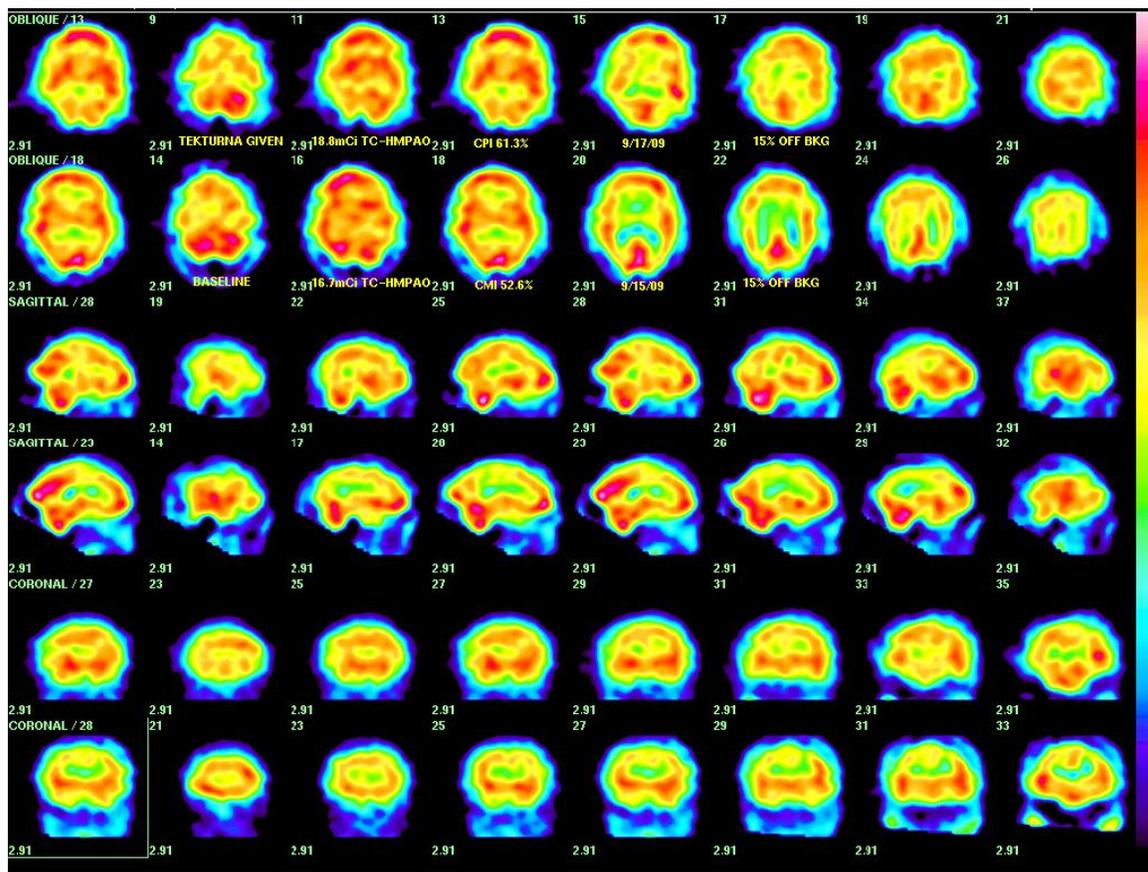


Same 46 year-old African American hyperthyroid woman whose abnormal thyroid scan is shown above, and whose metabolic stress images (upper of each set of 3 image pairs on the right) reveal a pseudoAlzheimer's pattern of decreased parieto-occipital, mesial temporal and periventricular hypometabolism more 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.

Control patient shows effect of antihypertensives as perfusion stimuli. Resting BP for the basal scan was 158/90 and for the stimulated scan two days later 148/90. This change in BP after aliskirin 300 mg oral daily and telemisartin 80 mg oral daily, which we have also observed within hours after acute BP control, is comparable to acute perfusion stimuli with 0.8 mg nitroglycerin sl, 500 mg acetazolamide IV, 100 mg cilostazol oral, 10 g omega-3 fish oil oral or 8 fl oz acai fruit juice, favoring a same day protocol without change in BP or other physiologic variables.



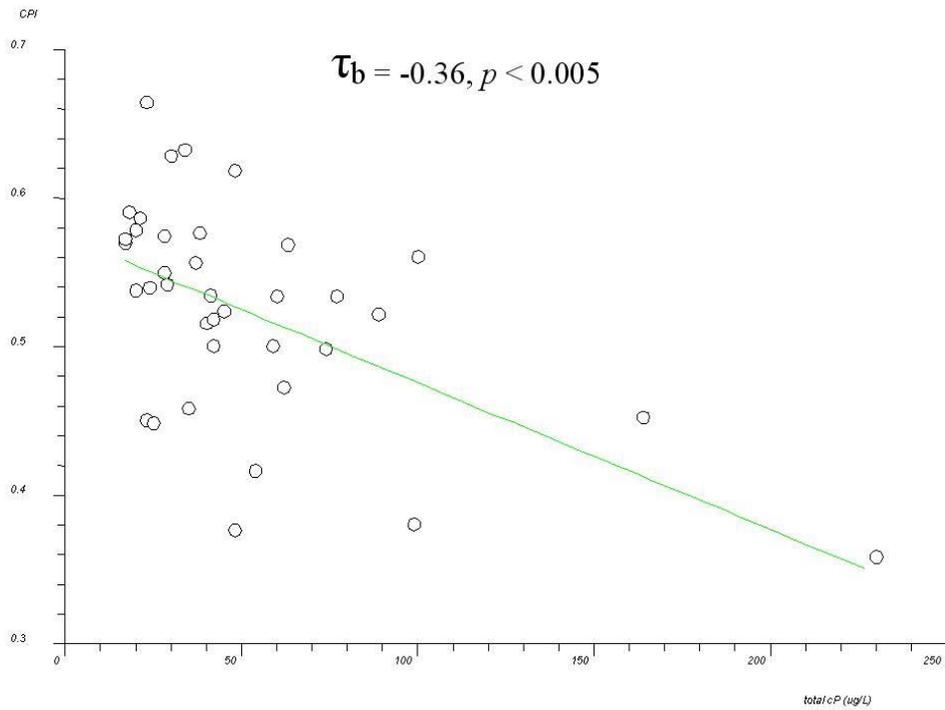
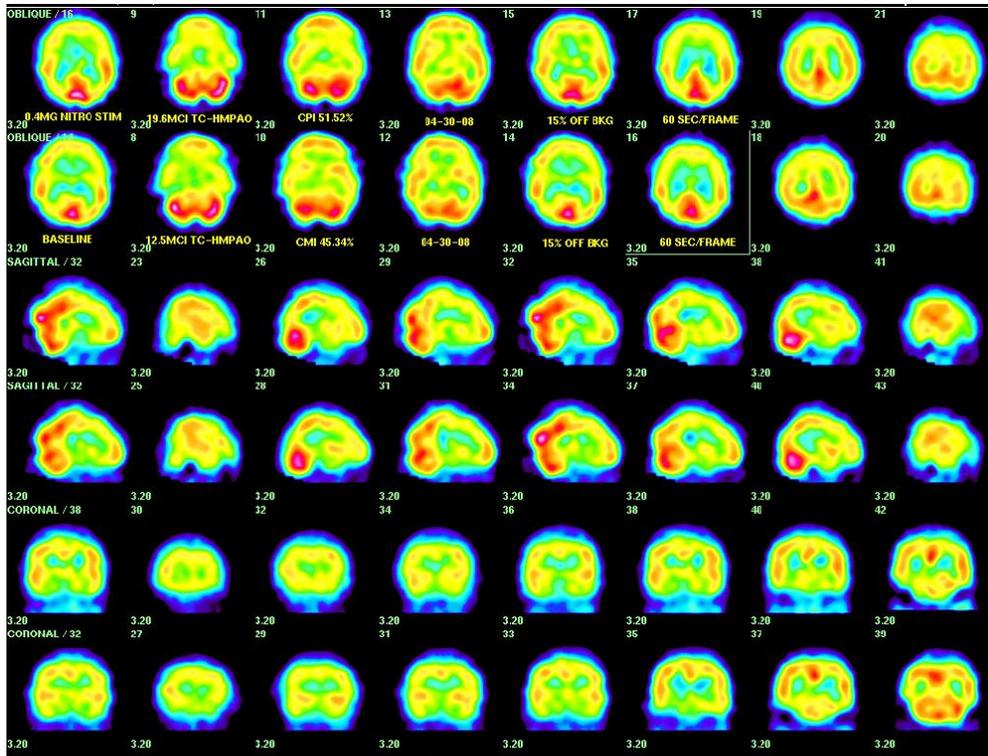
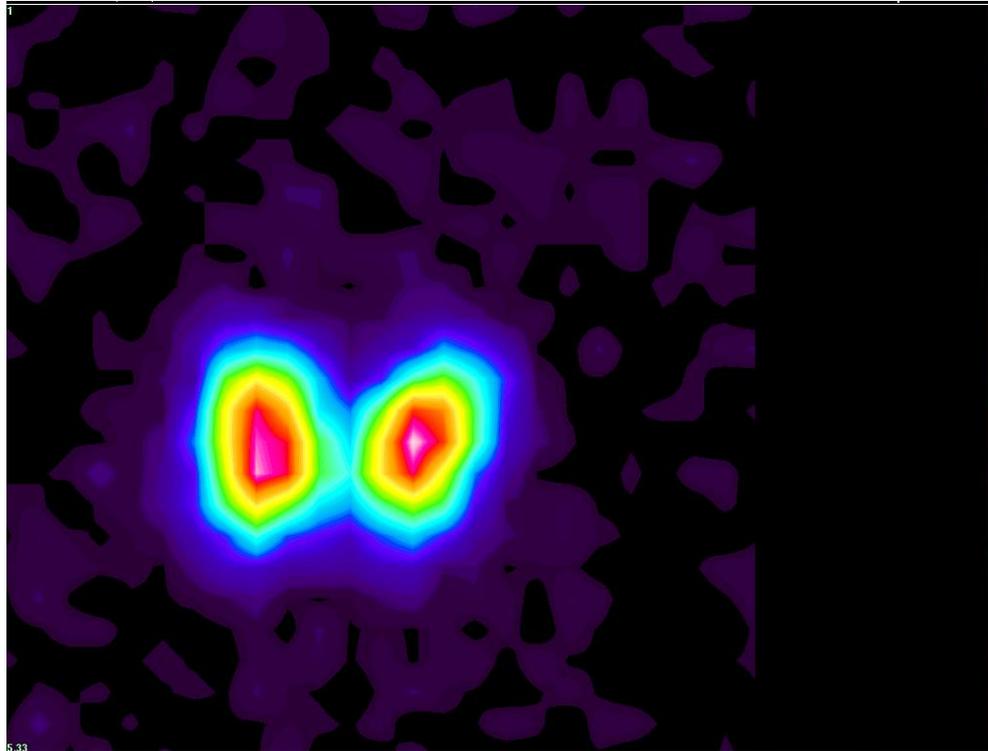


Figure 1. A summary of the relationship between total cP levels and CPI values among patients with thyroid dysfunction (n = 37) including hyperthyroid, hypothyroid and euthyroid chronic thyroiditis but excluding thyroid cancer and one outlier that did not affect statistical significance.



46 year-old woman with Graves' disease and bipolar 2 depression was euthyroid on lithium 300 mg po bid with RAIU 18% at 24 hr, FT4 0.86 mcg/dl (0.61-1.76) but complained of fatigue and memory loss, especially short term, and 8 months later had T3 thyrotoxicosis with T3 2.04 ng/ml (0.6-1.8), TSH < 0.01 requiring methimazole 5 mg po bid. Brain SPECT (above right) 2 months later, when she was again euthyroid (FT4 1.32, T3 1.18, TSH 1.63) with TYM 44/50 and had abnormal urine CPI 36 mcg/L (0-15) and CPIII 128 mcg/L (0-49) consistent with TyAsCI, shows patchy left temporal, bilateral mesial temporal, posterior periventricular, orbitofrontal and hypothalamic deficits without the usual precuneal hypoperfusion often seen in thyroid patients, which was present initially in the left posterior parietal cortex in this patient.

## 5.

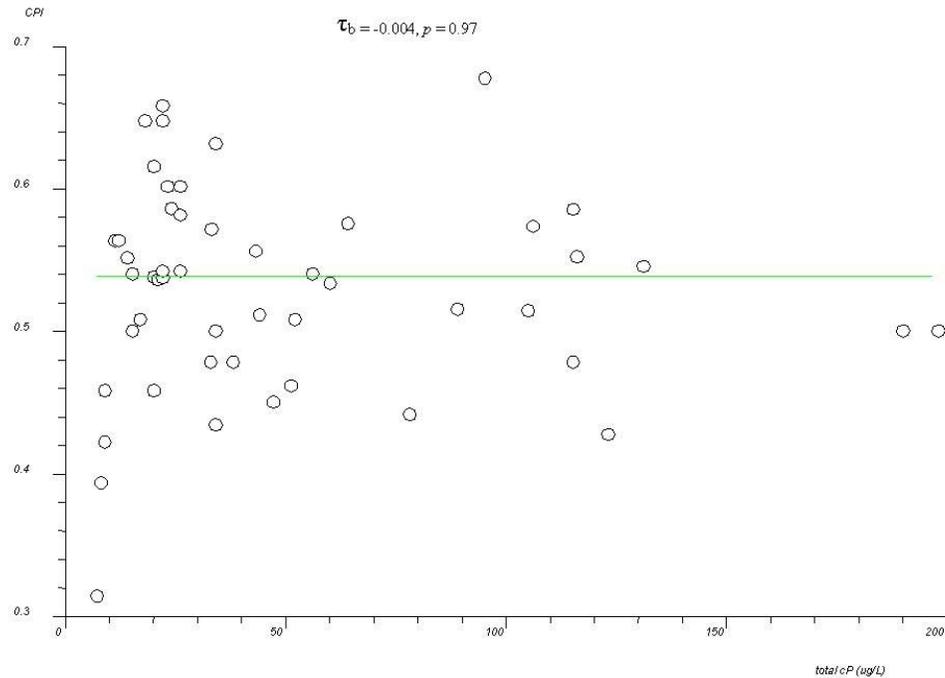
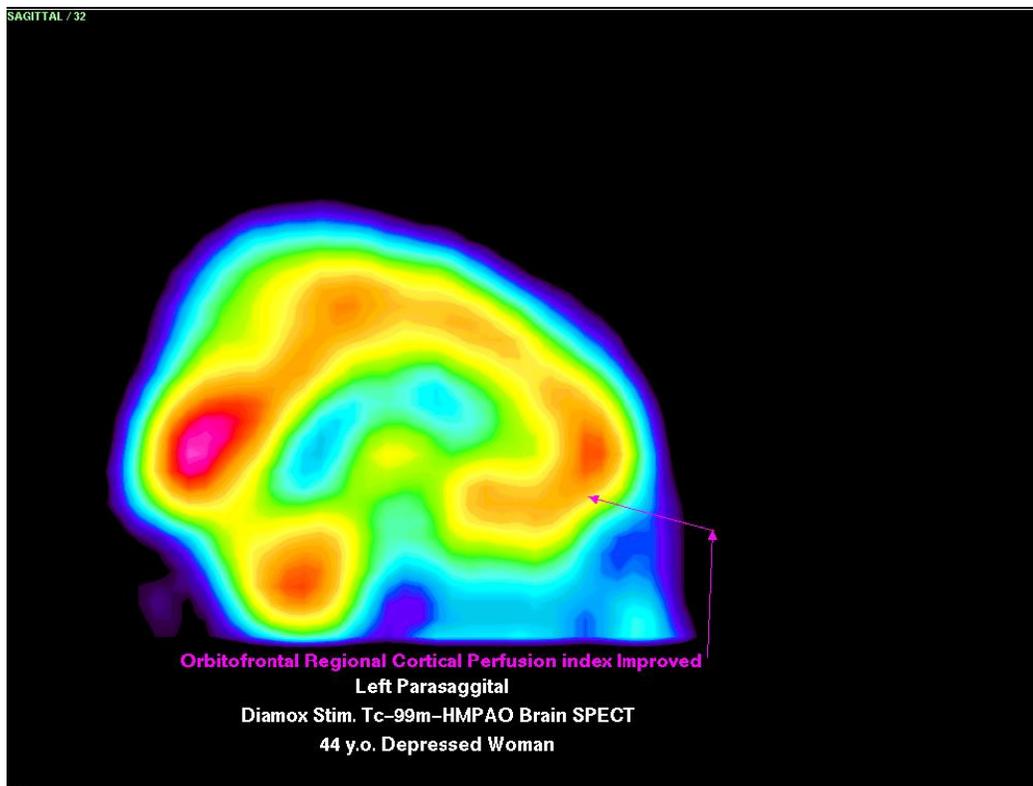


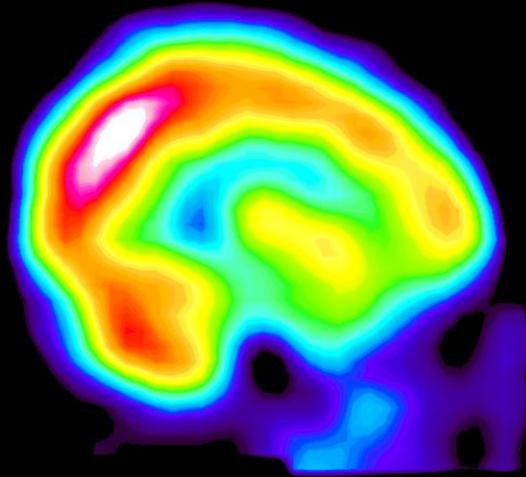
Figure 2. A summary of the relationship between total cP levels and CPI values among patients diagnosed with type 2 diabetes mellitus ( $n = 50$ ). The non-parametric linear regression statistic with a two-tailed  $P$ -value from StatsDirect (version 2.7.2) was utilized. The non-parametric linear regression statistic with a two-tailed  $P$ -value from StatsDirect (version 2.7.2) was utilized.

Patients with both thyroid disease and diabetes mellitus show relationships intermediate between those shown in Figure 1 and Figure 2 (data not shown).

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 of Thyroid Associated Cognitive Impairment (TyACI) eg. in patients with Hashimoto's encephalopathy, which we and others have also 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 juice of the acai berry (MonaVie) and most recently, cilostazol 100 mg oral, or effective antihypertensives, most recently aliskirin. This patient improved clinically with thionamide therapy and Bystolic, which may stimulate cerebral perfusion more than other beta blockers owing to a nitroglycerin-like effect.

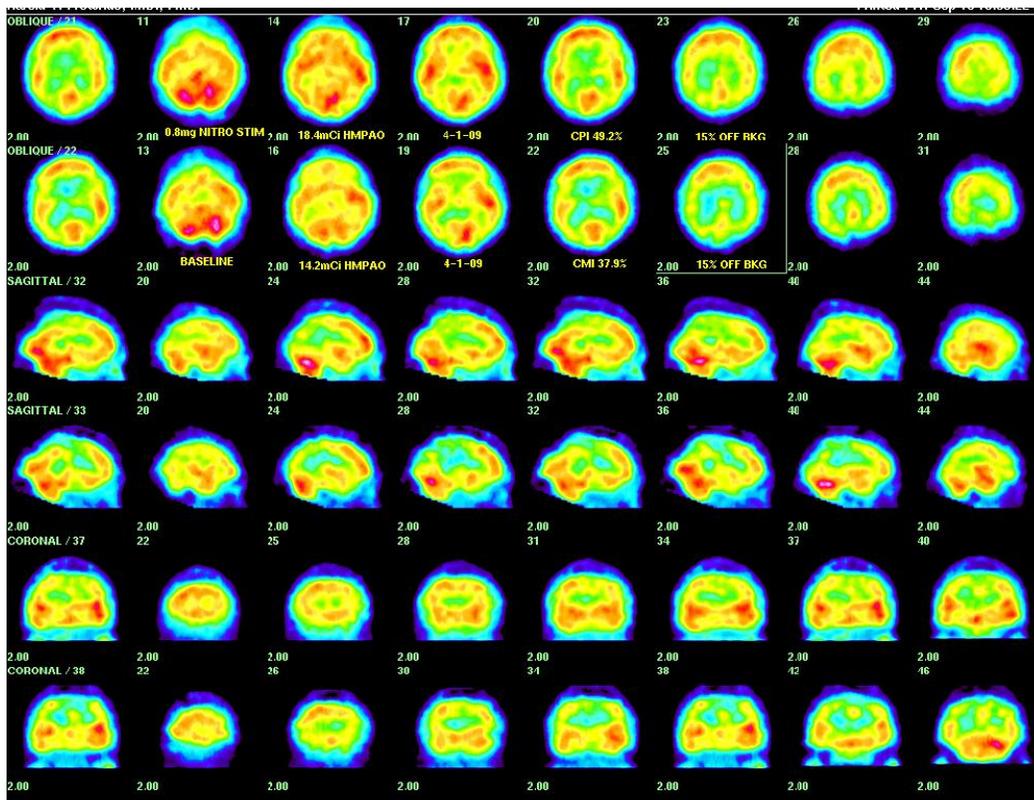




Left Parasagittal  
Tc-99m-ECD Basal Brain SPECT  
44 y.o. depressed woman

## 6.

44 year-old woman hypothyroid due to chronic thyroiditis with high prolactin, memory loss, unipolar depression and type 2 diabetes had CMi 30.3% and CPi 29.4%; porphyrins CpI 20; CpIII 11; uroporp 26; hepta 12 and marked cReact protein elevation 21.3.



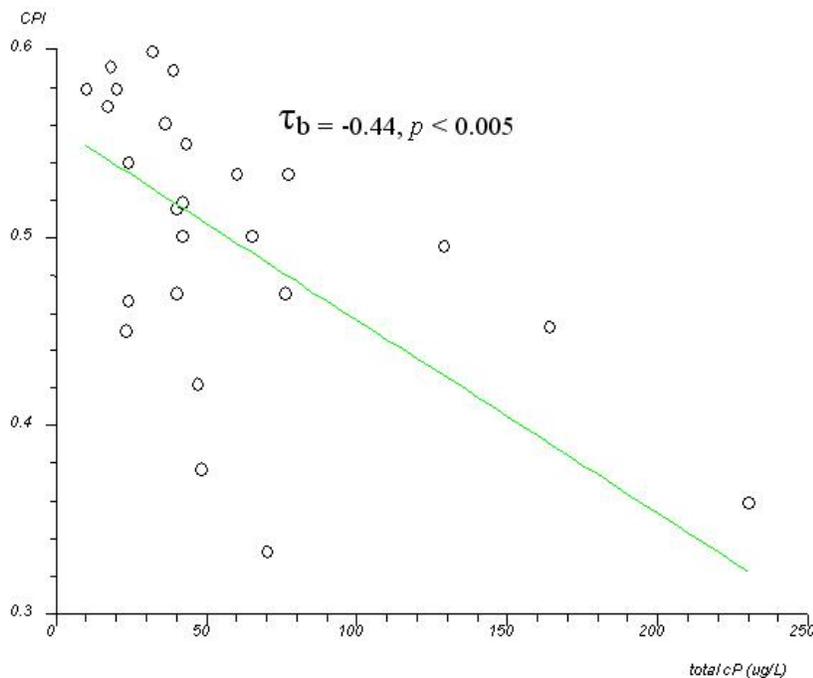
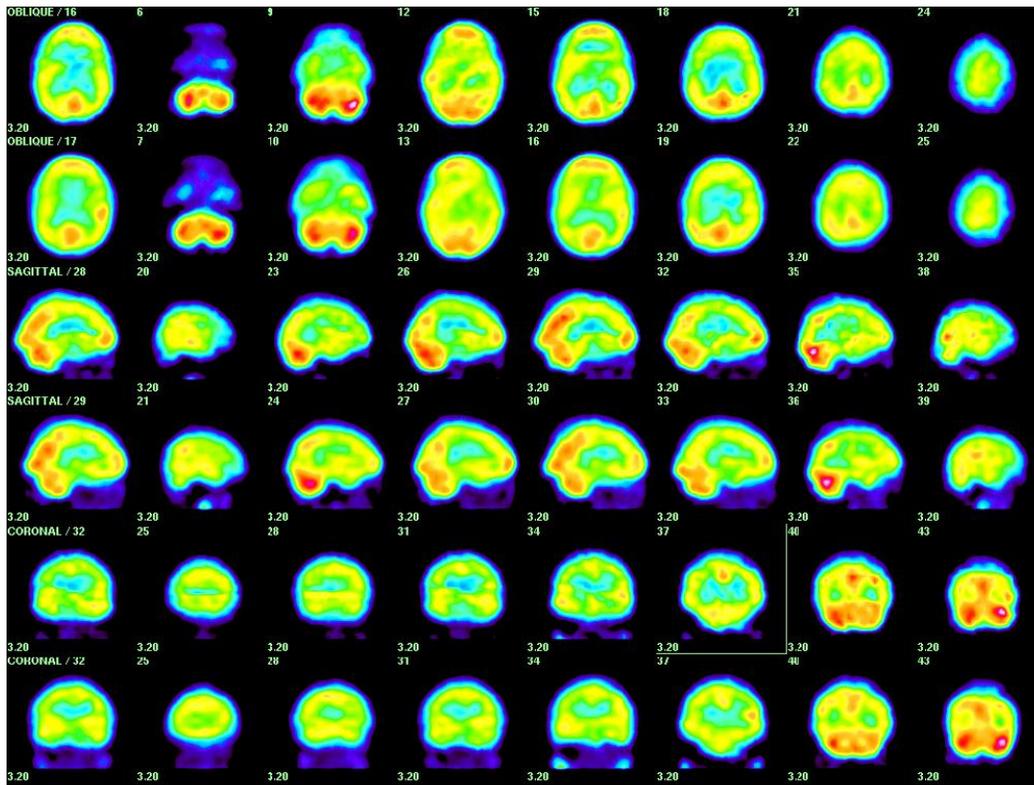


Figure 3: The non-parametric linear regression statistic with a two-tailed *P*-value from StatsDirect (version 2.7.2) was utilized.

<sup>1</sup> Including patients diagnosed with autism spectrum disorders, anxiety disorders, attention deficit disorders, depression disorders, bipolar disorders.

Depression in a woman with TSH in the upper half of the normal range whose CMI improved from 47.3% to 60.1% and CPI improved from 37.8% to 53.1% over 1 year therapy with clopidrogrel (Plavix) 75 mg po qd, rosuvastatin (Crestor), omega-3-marine oil (Lovaza) 4 g po qd. Therapy of MCI is U.S. FDA approved for at least one natural product: Cerefolin N-Acetyl-Cysteine. Our experience is mainly with renin-angiotensin-system inhibitors (eg. angiotensin converting enzyme inhibitors), acetyl cholinesterase inhibitors (eg. Aricept, Exelon), and cerebral perfusion stimulants (eg. cilostazol, Lovaza, nitrates). Improvements in Brain SPECT indices generally parallel functional cerebral measures such as neuropsychological test results or screening instruments such as the MiniMental Status Examination (MMSE) or Test Your Memory (TYM) tests.





## Summary

Nuclear medicine pharmacologic stress protocols further increase the high sensitivity of parametric perfusion-metabolic SPECT brain imaging. Comparison of basal metabolic and stimulated cerebral perfusion is particularly useful to assess vascular disease, which typically compromises perfusion reserve. Patients with normal cerebral perfusion reserve (CPI approx 5% > CMi) actually fare the worst with available therapies in our experience of over 15 years. Remarkably, patients with greater deficits in CPI vs. CMi (including those with CPI nearly equal to CMi) do the best with available therapy, which is arguably directed mainly toward improving cerebral hypoperfusion. Interestingly, the pseudo-Alzheimer's pattern of thyroid patients, which is frequently reversible, is often more pronounced in the stimulated perfusion rather than the basal metabolic images which are more typically abnormal in true Alzheimer's. As we and others reported previously, mixed dementia is much more common in everyday clinical practice than essentially pure Alzheimer's dementia. Further mechanisms of cerebral injury with potential for evolving therapy include toxic metal exposure (eg. Hg, Pb, Al, As) which we monitored with quantitative fractionated urine porphyrins, found associated with thyroid-related but generally not diabetes-related psychiatric disease, particularly bipolar depression, and treated with dimethyl propane sulfonate DMPS, nearly always compounded as suppositories of approximately 600 mg dose. Neurosteroid and other metabolic stressors such as hypothyroidism (typically associated or antecedent to Hashimoto's encephalopathy) or hyperthyroidism, which often (350% increase over basal rate) precedes thyroid-related Alzheimer's Disease (TyRAD), also provide an opportunity to investigate neuroendocrine mechanisms of pathophysiology.

Future developments include refinement of a thyroid and cerebral metabolic probe invented initially with Professor John Idoine to screen for TyRAsCI, TyRAD and other dementias, which remarkably may be adapted for cost-effective screening for thyroid cancer, currently one of the most important cancers in terms of increasing incidence and prevalence whose potential association with cognitive impairment remains essentially unexplored.