Clinical Nuclear Neurology:
Dementia, Parkinsonism, Epilepsy & Traumatic Brain Injury; How to get or do Nuclear Neurology

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Conflicts of Interest: None
Disclosures: None

Educational Objectives

- Know what kind of Nuclear Neurology studies and radiopharmaceuticals are currently available to help manage patients
- Understand what clinical questions can be addressed in different neurologic diseases by clinically available PET and SPECT
- Decide how best to incorporate Nuclear Neurology into clinical practice

Diseases Most Common in My Nuclear Neurology Practice

- Cognitive Impairment, Dementia: neurodegenerative, vascular, psychiatric
- Movement Disorders: parkinsonism
- Neuro-Oncology
- Cerebrovascular Disease
- Epilepsy
- CSF-related: NPH, leaks, blocks
- Traumatic Brain Injury

TABLE 12-1 Indications for Clinically Available Neuromolecular Imaging Tests

Disorder	Indications	PET	SPECT
Dementia	Early diagnosis, differential diagnosis	FDG	Bicisate, exametazime
Brain tumors	Grading, staging, tumor localization, mass lesion diagnosis, tumor recurrence versus treatment effect, therapy efficacy evaluation, malignant degeneration diagnosis, prognostication	FDG	Thallium
Epilepsy	Episodic neurologic syndrome diagnosis, localization of seizure focus	FDG	Bicisate, exametazime
Parkinsonism	Early diagnosis, differential diagnosis	FDG	Ioflupane, bicisate, exametazime
Cerebrovascular disease	Cellular viability, cellular ischemia		Bicisate
Traumatic brain injury	Injury identification	FDG	Bicisate

FDG = fludeoxyglucose; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

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- CSF NPH, flow, leak, block, shunt patency NA Pertechnetate DTPA In 111

Clinical Brain PET Radiopharmaceuticals

- [^{18}F]FDG: Glucose metabolism, universal; Neuronal viability; Ischemia-induced increased anaerobic glycolysis
- Amyloid imaging PET – Available, paid for only under CED (research project)
- [^{18}F]Flortaucipir – tau deposit imaging
- [^{13}N]NH3: CBF in 1980s; aNDA
- [^{11}C]Flumazenil: Neuronal viability, NA
- [^{15}O]H2O: NA

Amyloid Imaging, FDA-approved, CMS-not approved

- CMS: Coverage with Evidence Development (CED)
- [^{18}F]florbetapir
- [^{18}F]florbetaben
- [^{18}F]flutemetamol

Clinical Brain Nuclear & SPECT Radiopharmaceuticals

- Perfusion tracers: [^{99m}Tc]exametazine, [^{99m}Tc]bicisate
- [^{201}Tl]Thallous Chloride: Brain tumor sensivity & specificity reported in the 80% range
- DaTscan, [^{123}I]ioflupane: DA Transporter
- [^{111}In]DTPA: CSF Tracer

Nuclear Neurology (NN)

- Cerebral Perfusion SPECT – Neurolite, Ceretec; clinically available
- Glucose Metabolism PET – FDG; clinically available
- Amyloid imaging PET – few; clinically available, not paid for
- Tau imaging PET – Very recently available
- Neurochemical/Neurotransmitter imaging, SPECT/PET – Fluorodopa, DAT available

Basis of Imaging Signal

- CTP, MR PWI, fMRI, U/S are all lumen-based imaging
- SPECT and PET (NN) is cell-based
- If there are no cells, there is no NN signal
- Uptake into the cell provides cell status information; this many times is not obtained from a lumen-based proxy modalities
- Greater sensitivity in diagnosis

Cerebral Perfusion SPECT (CPS)

Shows 2 phenomena:

1. Status of the plumbing, ie. vascular system
2. Neuronal Work, ie. synaptic activity

- Due to coupling between neuronal activity, perfusion and metabolism

Cerebral Metabolism (FDG-PET)

Shows 2 phenomena:

1. Viability and status of the brain cell
2. Neuronal Work, ie. synaptic activity, network activation

- Due to coupling between neuronal activity, perfusion and metabolism

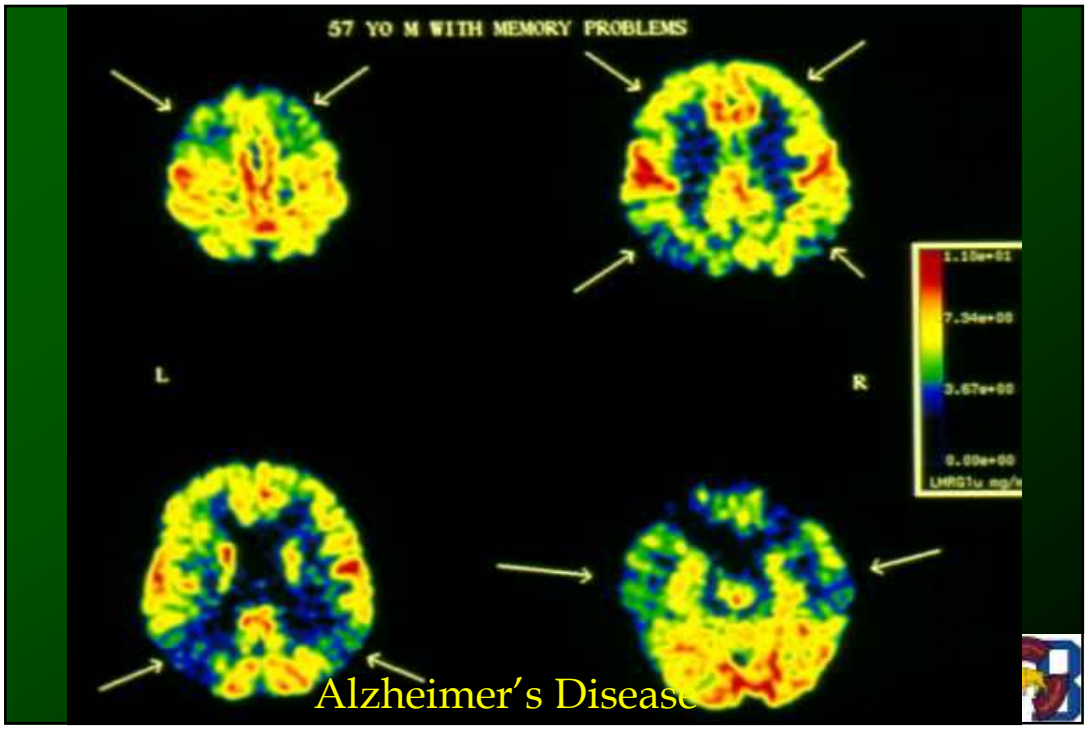
Decreased FDG-PET Signal Comes From:

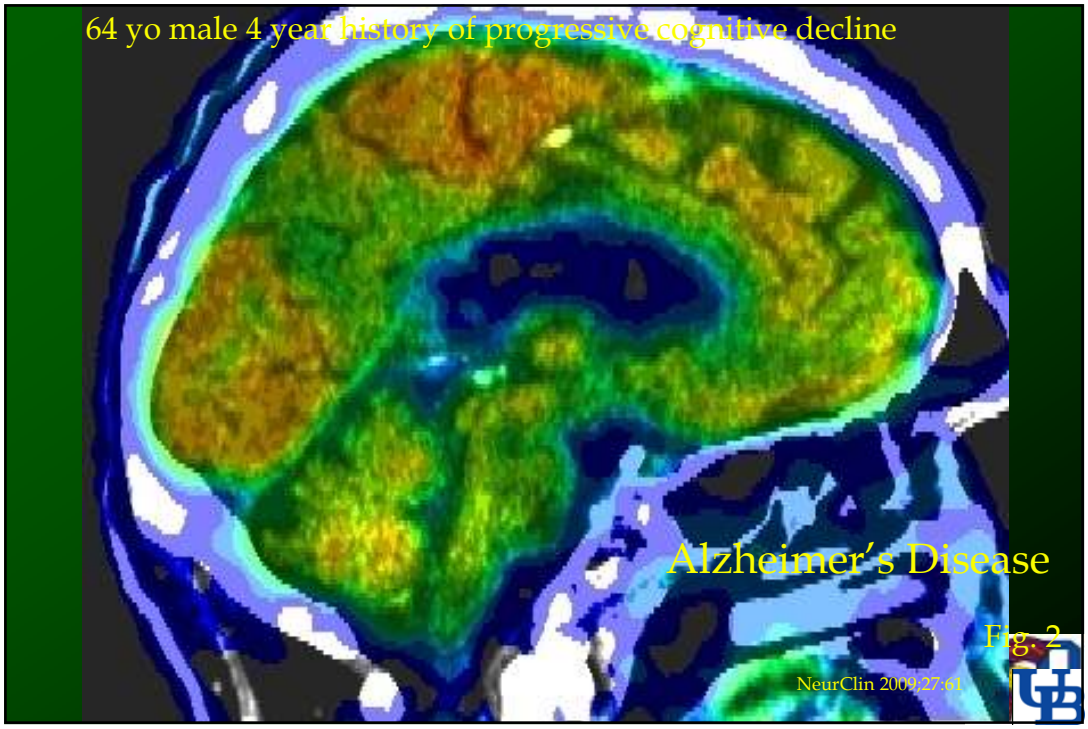
- Cell loss
- Synapse loss
- Tissue atrophy
- Decreased synaptic activity
- Diaschisis – disruption of neuronal network functioning

Cognitive Impairment, Dementia: Alzheimer's, Other Neurodegenerative, Vascular, Psychiatric

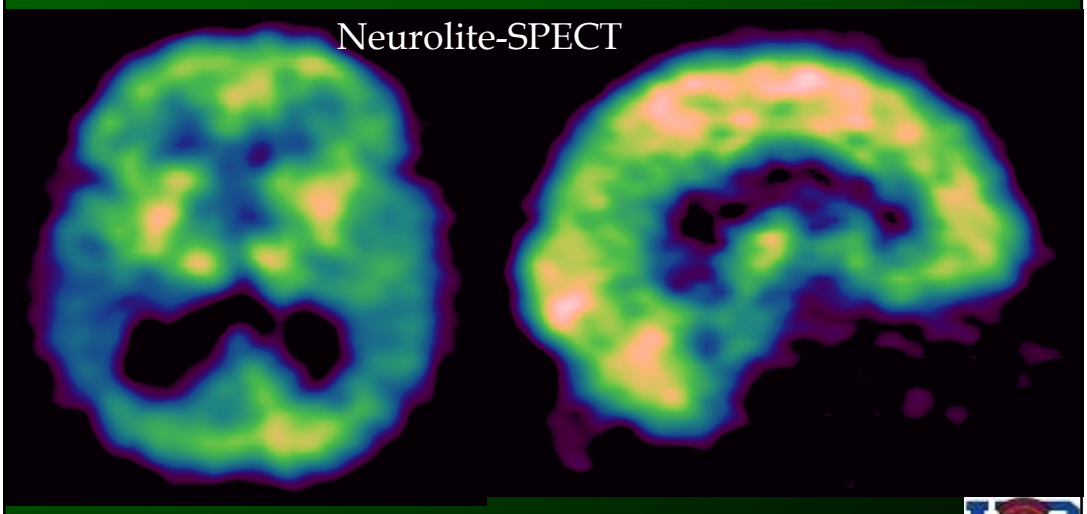
Dementia/MCI differential diagnosis in my clinical practice

- Small vessel disease (SVD)
- Alzheimer disease (AD)
- Dementia with Lewy bodies (DLB)
- Psychiatric illness (PSYC)
- Frontotemporal lobar degeneration (FTLD)
- Other cerebrovascular syndromes (CVD)
- Normal pressure hydrocephalus (NPH)
- Other neurodegenerative diseases (NDGN)
- Toxic and metabolic dementias (TME)
- Parkinson's Disease (PD)
- Atypical Parkinsonism (PD+)


57 YO M WITH MEMORY PROBLEMS
L
R
Alzheimer's Disease


64 yo male 4 year history of progressive cognitive decline
Alzheimer's Disease
Fig. 2
NeurClin 2009;27:61

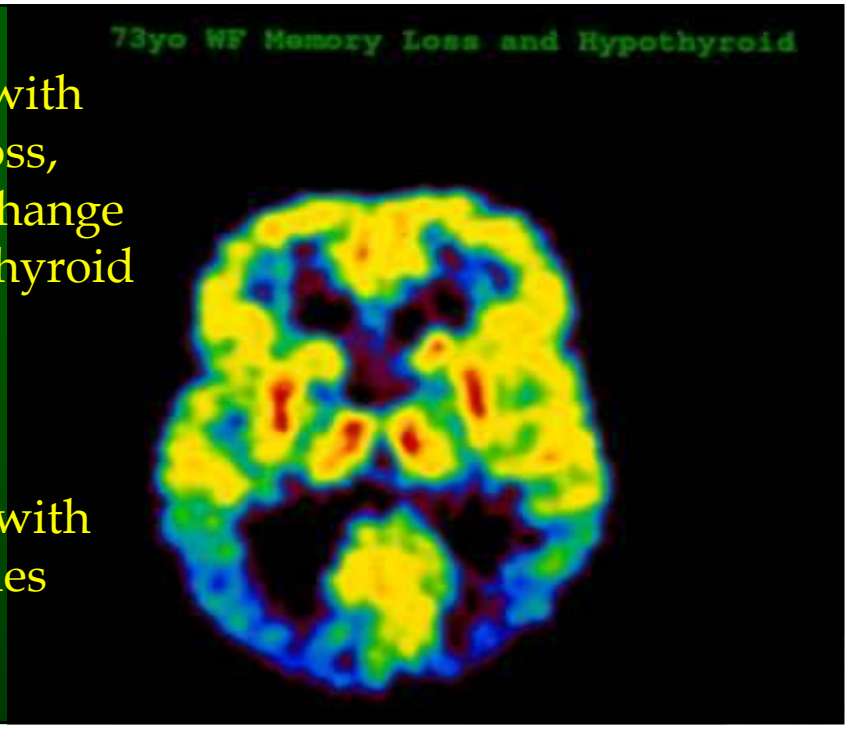
70 yo female: memory and language problems



Prob. Alzheimer's Disease

U1498

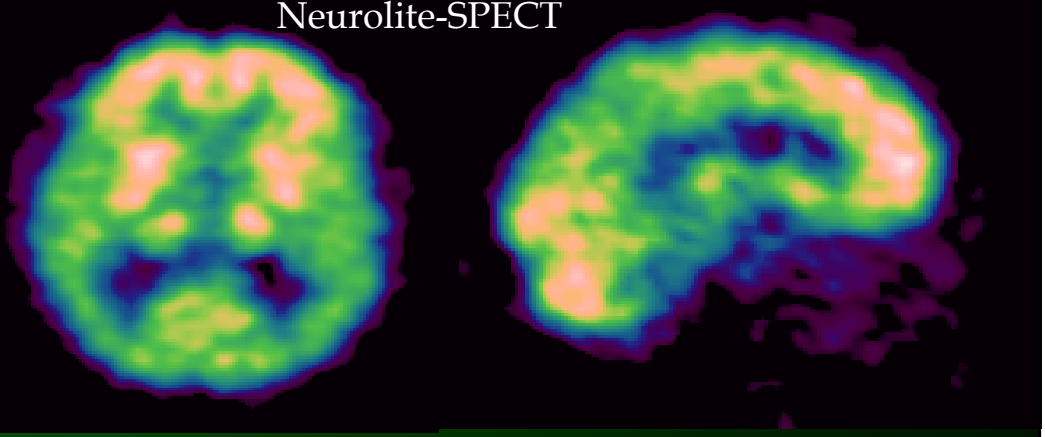
73 yo WF with memory loss, behavior change and hypothyroid



Dementia with Lewy Bodies

87 yo male: MCI, tremor, parkinsonism, gait impairment, hydrocephalus

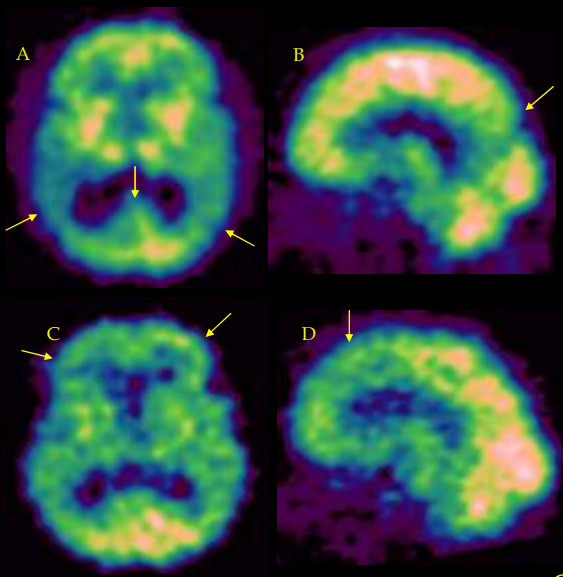
Neurolite-SPECT



Lewy Body Disease

U1512

Bicisate-SPECT



R

L

Alzheimer's Disease

Frontotemporal Dementia

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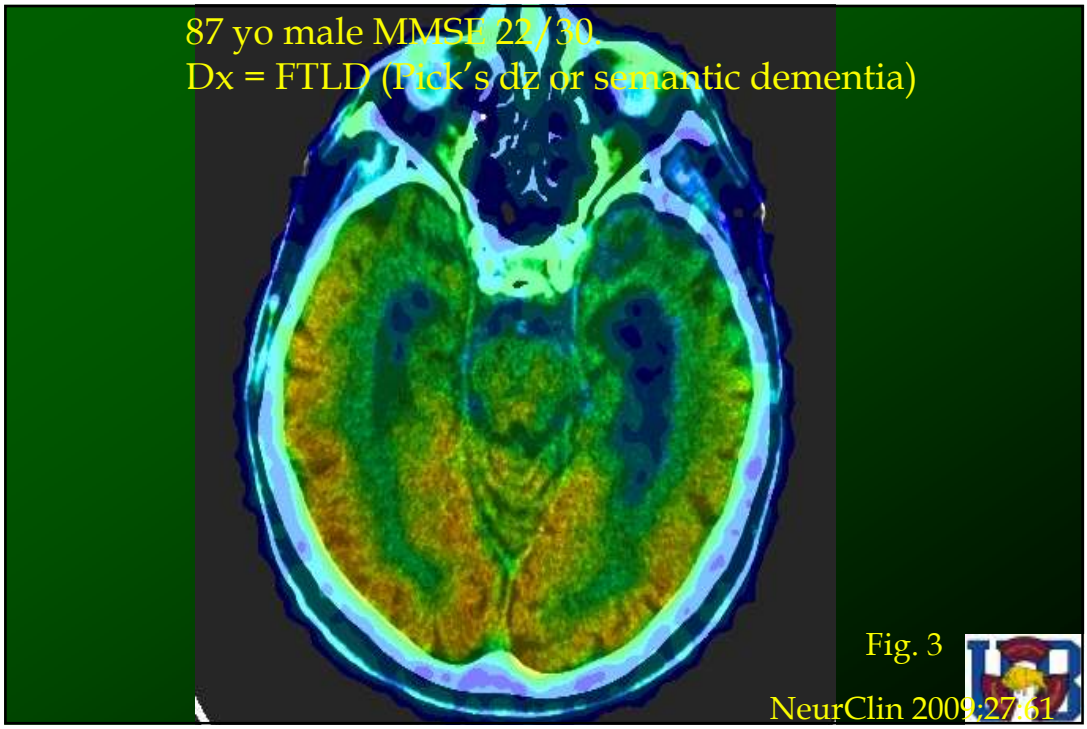
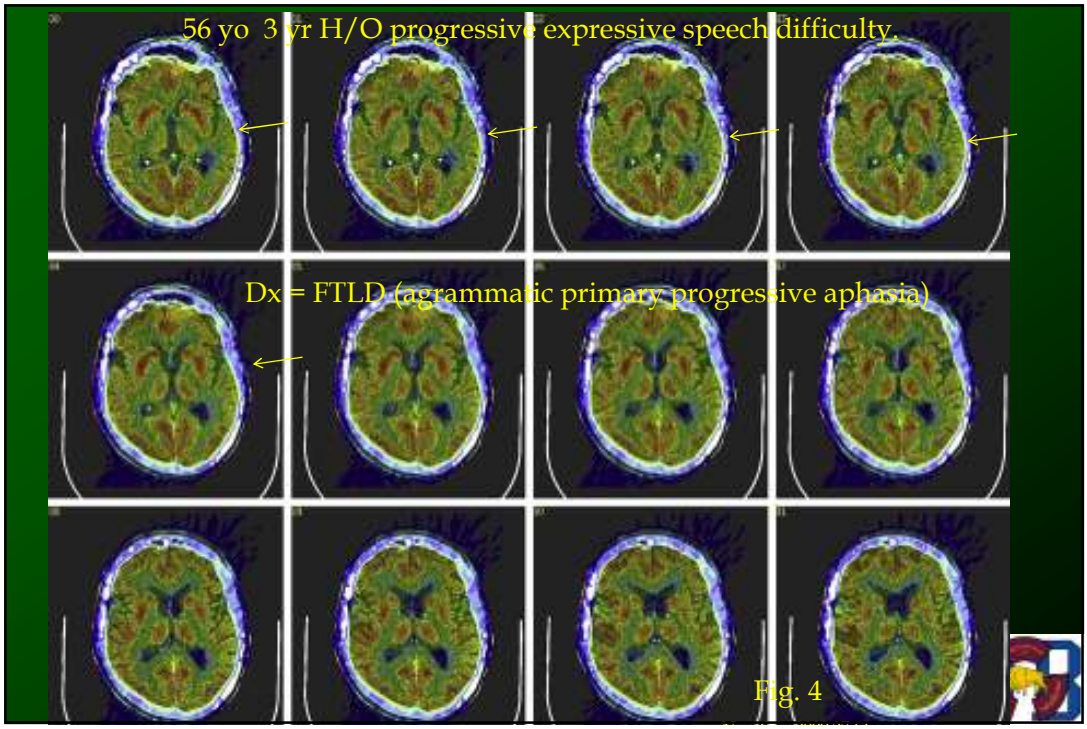
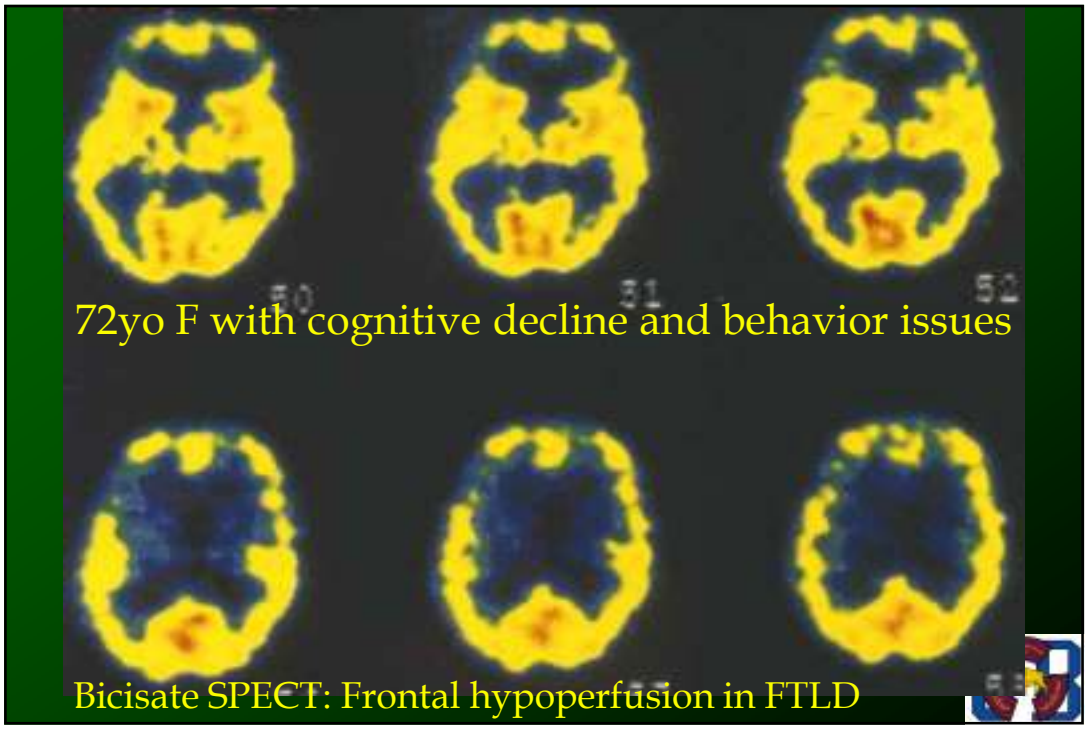
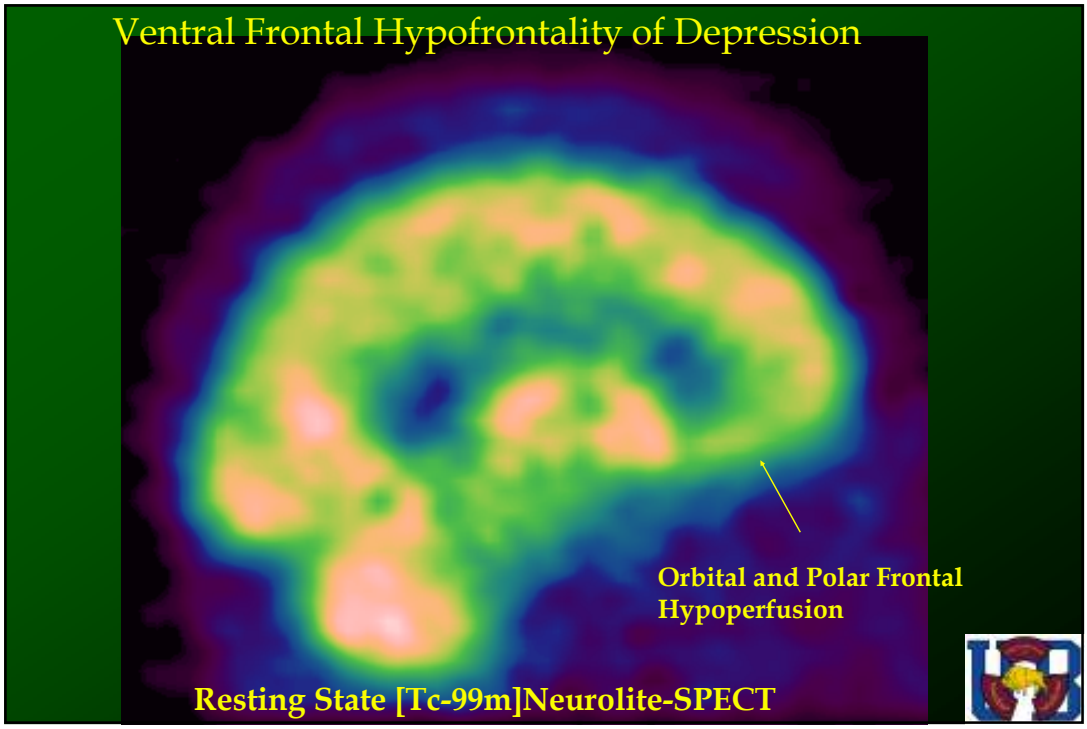
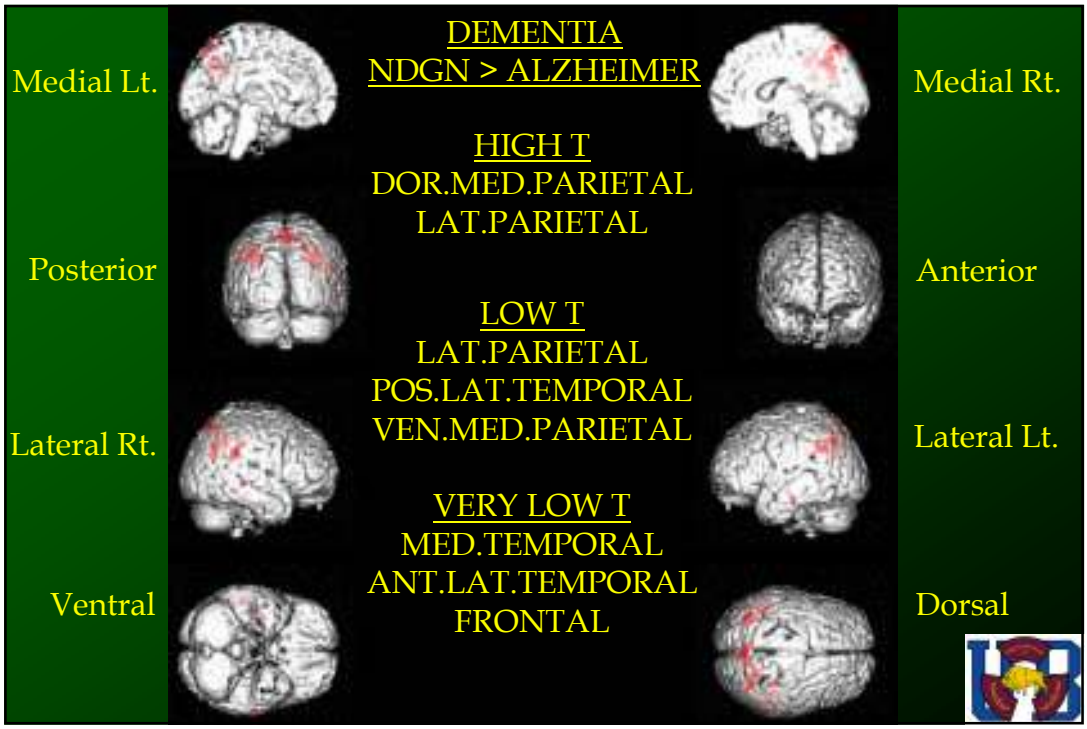
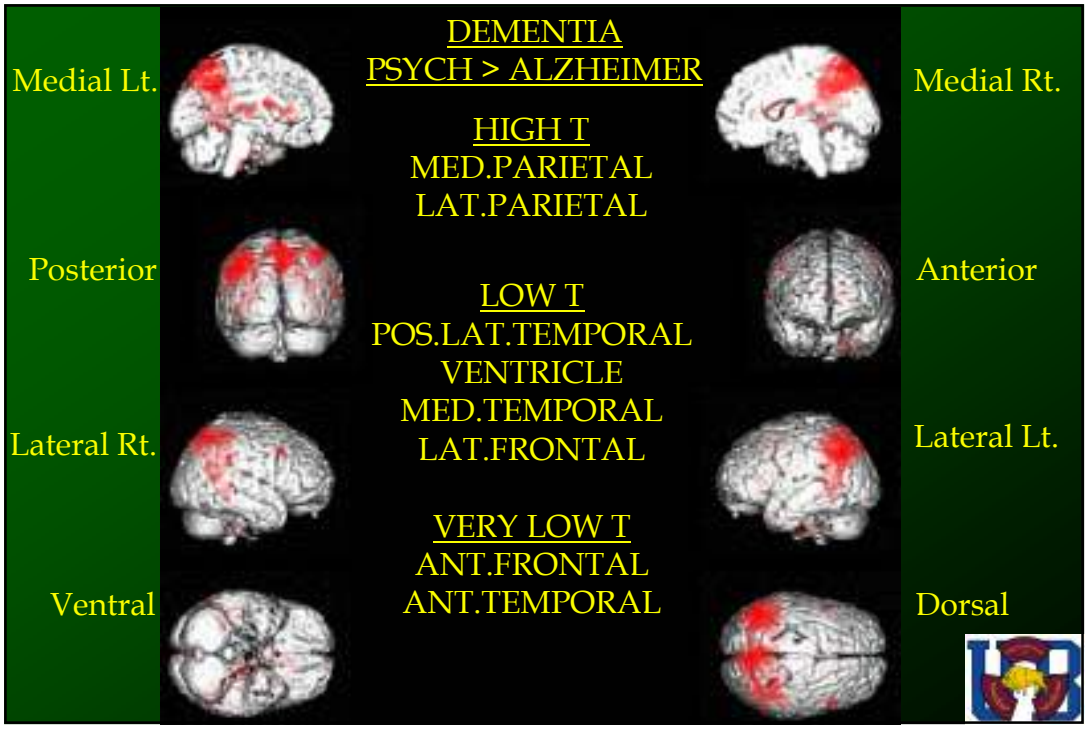

87 yo male MMSE 22/30.
Dx = FTLD (Pick's dz or semantic dementia)
Fig. 3
NeurClin 2009;27:61

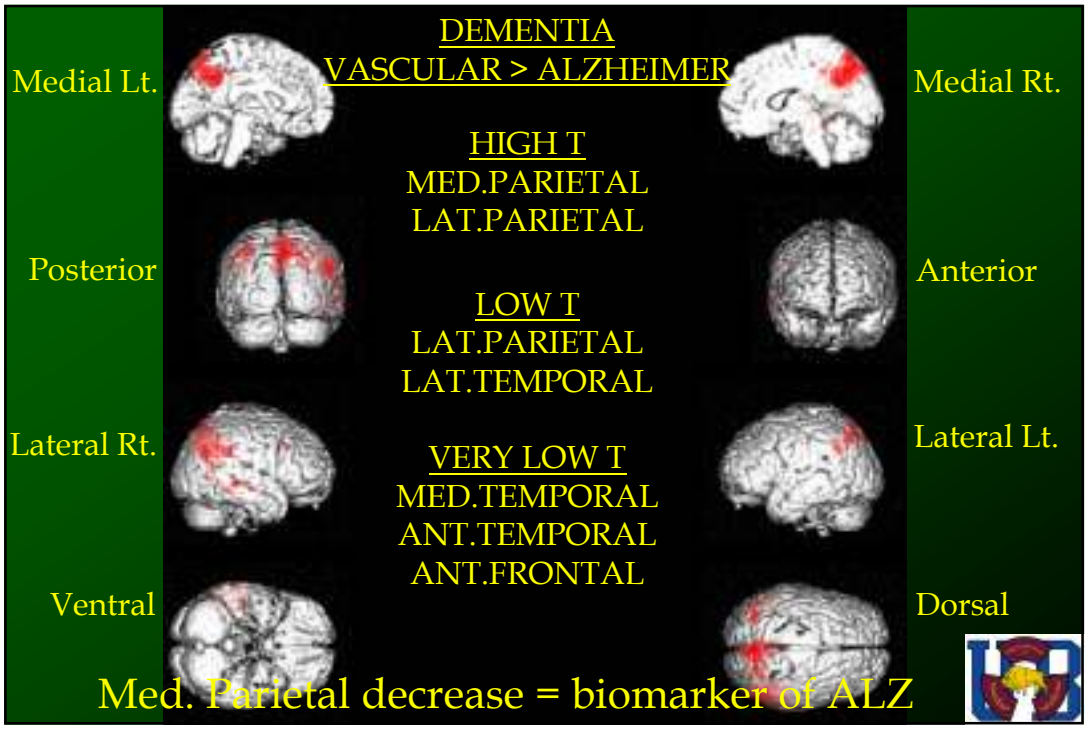

56 yo 3 yr H/O progressive expressive speech difficulty.
Dx = FTLD (agrammatic primary progressive aphasia)
Fig. 4

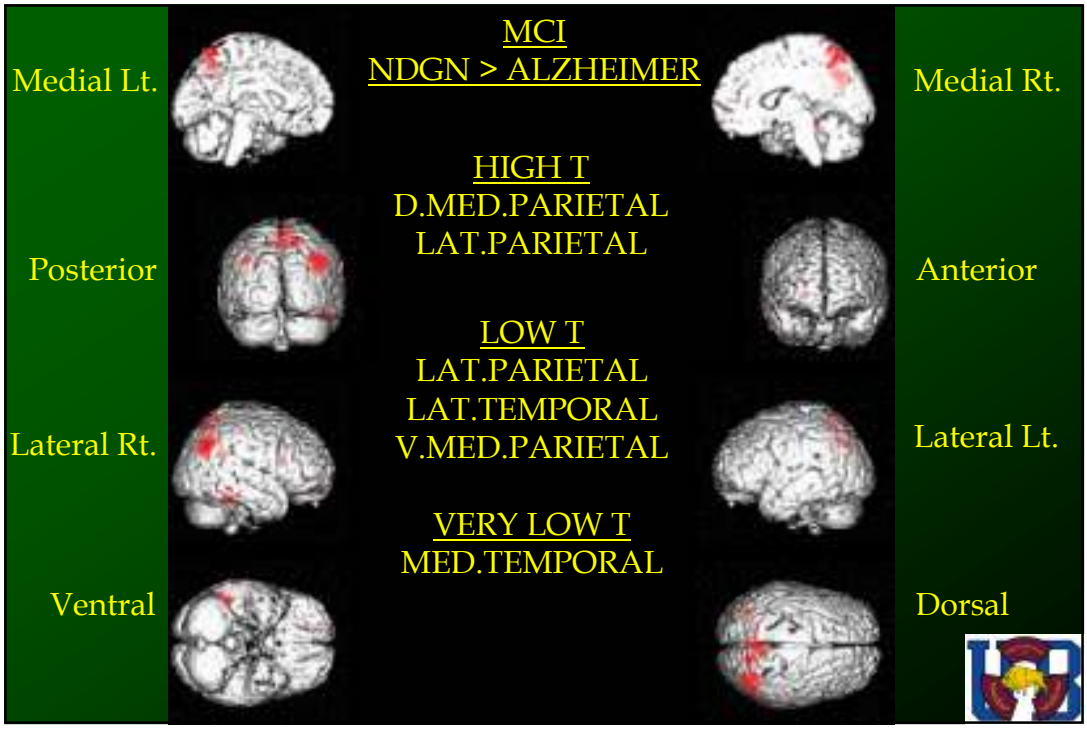

72yo F with cognitive decline and behavior issues
Bicisate SPECT: Frontal hypoperfusion in FTLD

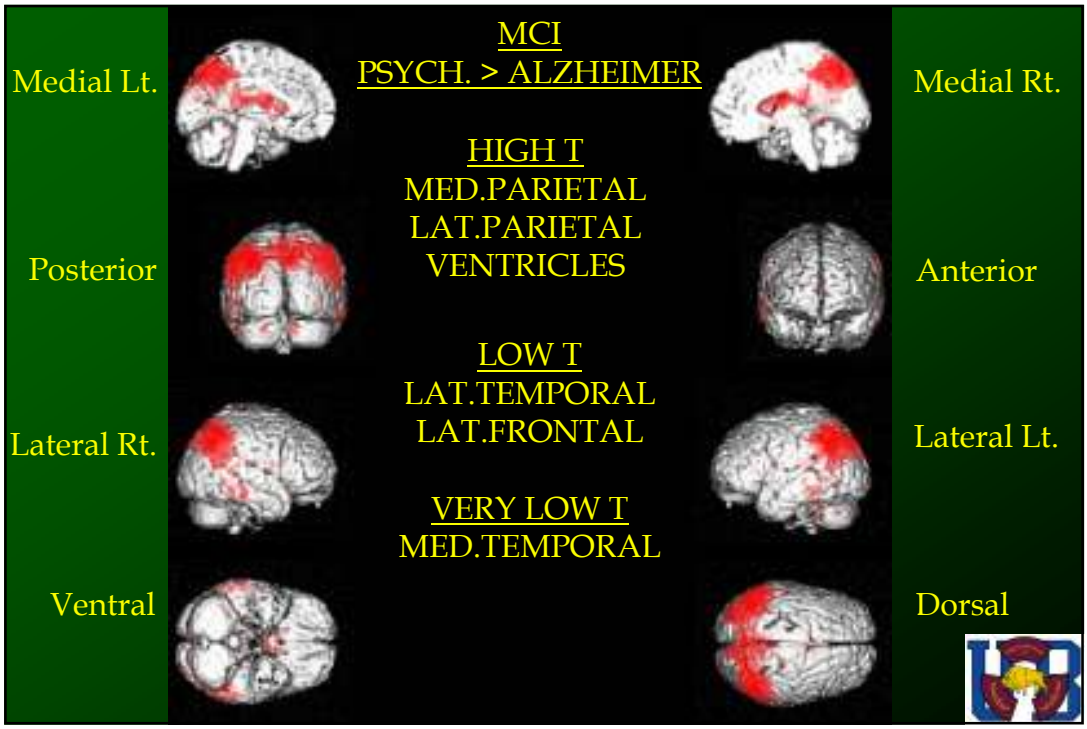

Ventral Frontal Hypofrontality of Depression
Orbital and Polar Frontal Hypoperfusion
Resting State [Tc-99m]Neurolite-SPECT

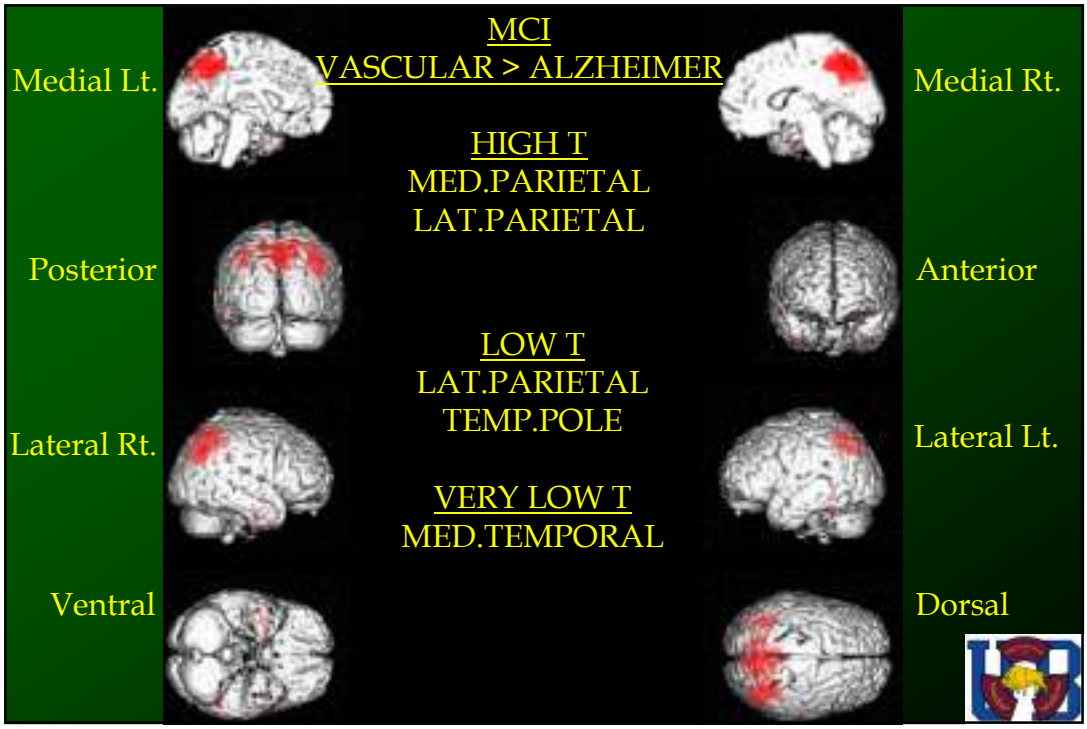

Medial Lt.
Medial Rt.
Posterior
Anterior
Lateral Rt.
Lateral Lt.
Ventral
Dorsal
DEMENTIA
NDGN > ALZHEIMER
HIGH T
DOR.MED.PARIETAL
LAT.PARIETAL
LOW T
LAT.PARIETAL
POS.LAT.TEMPORAL
VEN.MED.PARIETAL
VERY LOW T
MED.TEMPORAL
ANT.LAT.TEMPORAL
FRONTAL

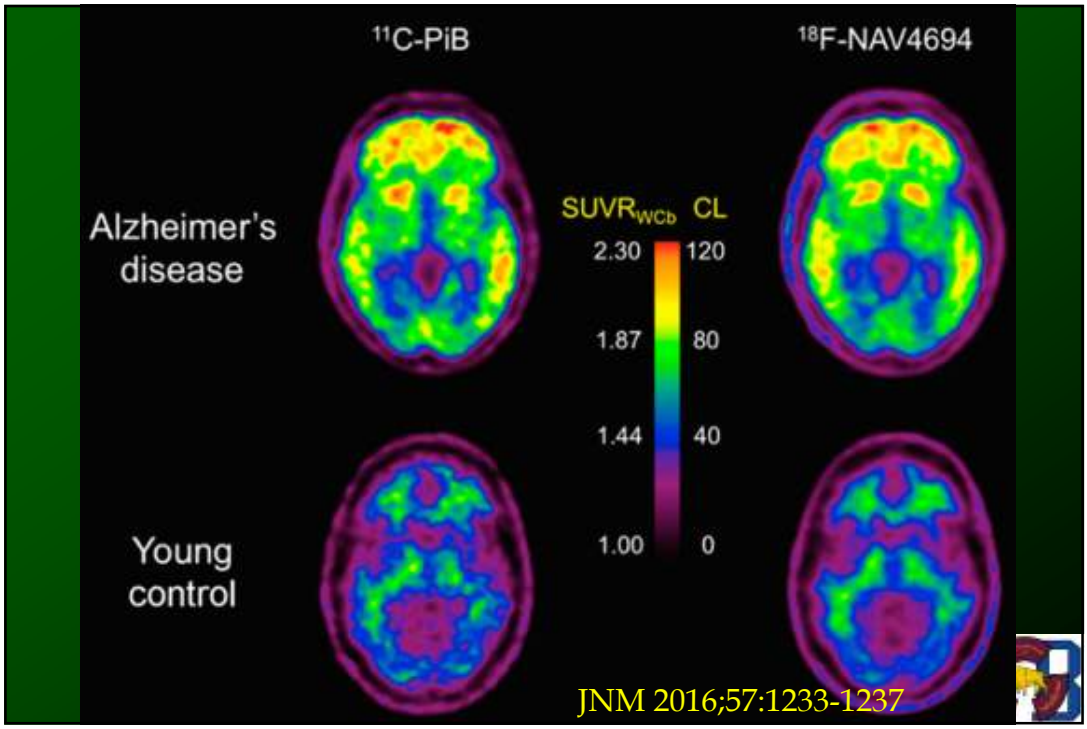

Medial Lt.
Medial Rt.
Posterior
Anterior
Lateral Rt.
Lateral Lt.
Ventral
Dorsal
DEMENTIA
PSYCH > ALZHEIMER
HIGH T
MED.PARIETAL
LAT.PARIETAL
LOW T
POS.LAT.TEMPORAL
VENTRICLE
MED.TEMPORAL
LAT.FRONTAL
VERY LOW T
ANT.FRONTAL
ANT.TEMPORAL

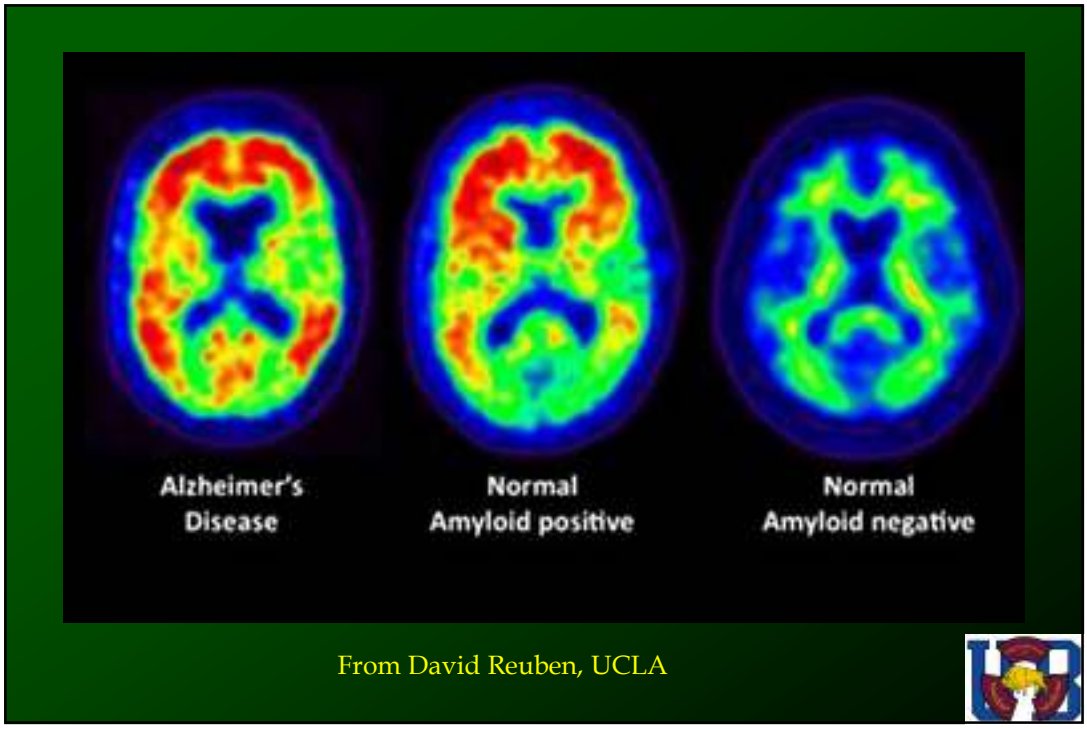

DEMENTIA
VASCULAR > ALZHEIMER
HIGH T
MED.PARIETAL
LAT.PARIETAL
LOW T
LAT.PARIETAL
LAT.TEMPORAL
VERY LOW T
MED.TEMPORAL
ANT.TEMPORAL
ANT.FRONTAL
Medial Lt.
Medial Rt.
Posterior
Anterior
Lateral Rt.
Lateral Lt.
Ventral
Dorsal
Med. Parietal decrease = biomarker of ALZ


MCI
NDGN > ALZHEIMER
HIGH T
D.MED.PARIETAL
LAT.PARIETAL
LOW T
LAT.PARIETAL
LAT.TEMPORAL
V.MED.PARIETAL
VERY LOW T
MED.TEMPORAL
Medial Lt.
Medial Rt.
Posterior
Anterior
Lateral Rt.
Lateral Lt.
Ventral
Dorsal

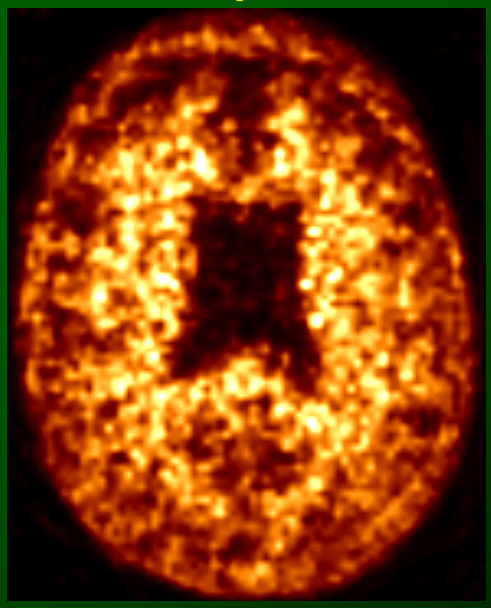

MCI
PSYCH. > ALZHEIMER
HIGH T
MED.PARIETAL
LAT.PARIETAL
VENTRICLES
LOW T
LAT.TEMPORAL
LAT.FRONTAL
VERY LOW T
MED.TEMPORAL
Medial Lt.
Medial Rt.
Posterior
Anterior
Lateral Rt.
Lateral Lt.
Ventral
Dorsal


MCI
VASCULAR > ALZHEIMER
HIGH T
MED.PARIETAL
LAT.PARIETAL
LOW T
LAT.PARIETAL
TEMP.POLE
VERY LOW T
MED.TEMPORAL
Medial Lt.
Medial Rt.
Posterior
Anterior
Lateral Rt.
Lateral Lt.
Ventral
Dorsal

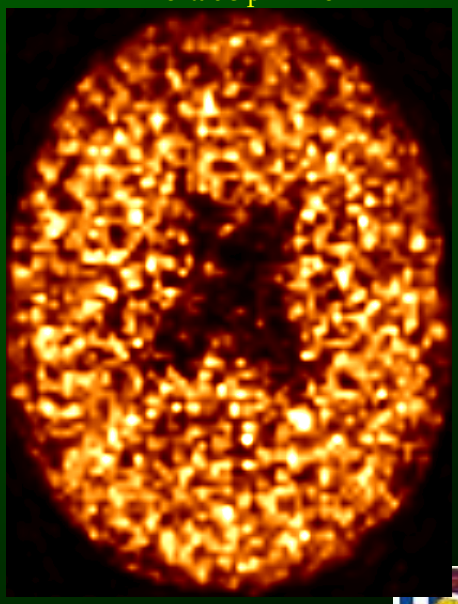

11C-PiB
18F-NAV4694
Alzheimer's disease
Young control
SUVRWCb
CL
2.30
120
1.87
80
1.44
40
1.00
0
JNM 2016;57:1233-1237


Alzheimer's Disease
Normal Amyloid positive
Normal Amyloid negative
From David Reuben, UCLA

Florbetapir F 18

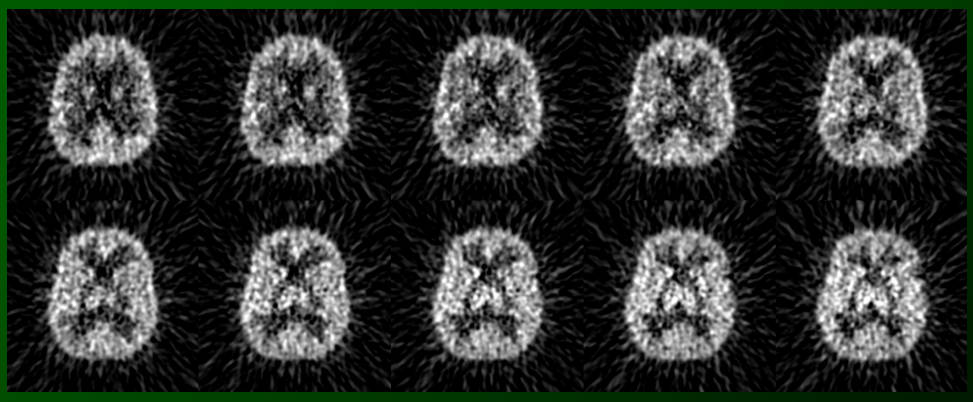


Flortaucipir F 18

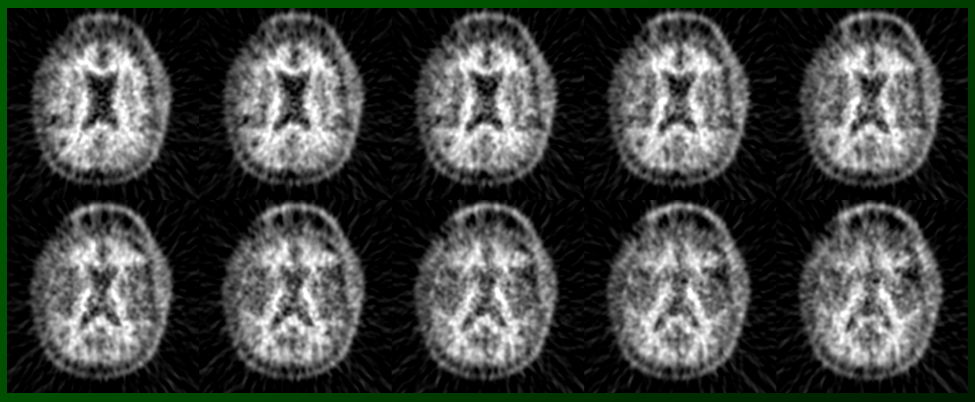


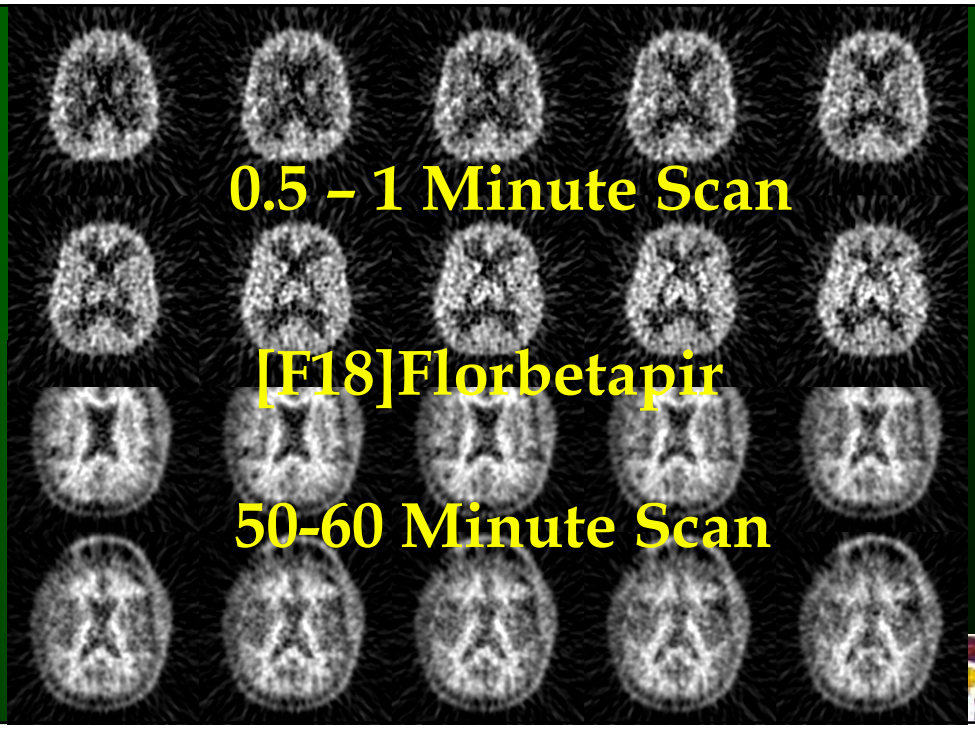
ADNI Study, Molecular Diagnostics (RSM's lab)

[O-15]H2O Blood Flow PET?



T1WSE MRI?





Danger, Will Robinson!

- Know the disease
- Know the radiopharmaceutical
- Know how the study was performed

Amyloid or Glucose Metabolism Imaging?

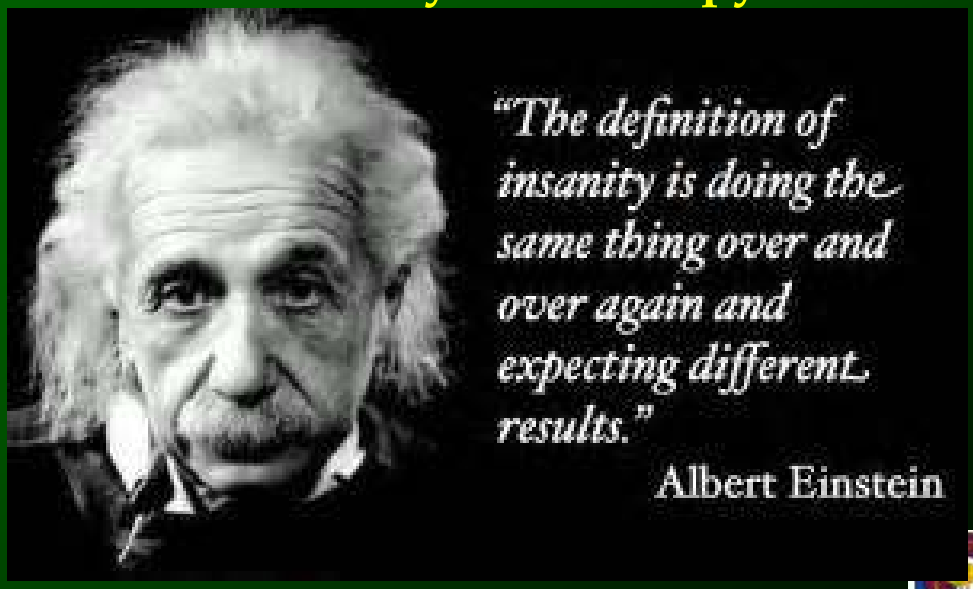
Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-190220
IOS Press

^{18}F-FDG Is a Superior Indicator of Cognitive Performance Compared to ^{18}F-Florbetapir in Alzheimer's Disease and Mild Cognitive Impairment Evaluation: A Global Quantitative Analysis

Mohsen Khosravi[a], Jonah Peter[b], Nancy A. Wintering[c], Mijail Serruya[d], Sara Pourhassan Shamchi[b], Thomas J. Werner[b], Abass Alavi[b] and Andrew B. Newberg[c,d]

Conclusions: This study reveals how ^{18}F-FDG-PET global quantification is a superior indicator of cognitive performance in AD and MCI patients compared to ^{18}F-florbetapir PET. Accordingly, we still recommend ^{18}F-FDG-PET over amyloid imaging in the evaluation for AD and MCI.

Anti-Amyloid Therapy



NN Dementia Profiles I

- AD: Post. Dominant, Asym., Assoc. Cortex Dec., Medial Parietal Dec.Always
- DLB: CIS, Post. Assoc. and Occipital Dec., Striatal Inc., Early Frontal Inc.
- FTLD: Frontal &/or Temporal Dec. &/or Hemispheric Cortical/Subcort. Dec., Medial Frontal Dec. Always
- SVD: Patchy Cortical Dec., WM Dec. Always

NN Dementia Profiles II

- NPH: Diffuse Supratent. GM Dec., Spares Medial Occ.
- PD: Striatal Inc., Poss. Frontal Dec.
- PD+: Striatal & Frontal Dec.
- PSYC: Ventral & Medial Frontal Dec. OR Inc.
- TME: Patchy Cortical Dec.,Wide Distrib.
- TBI: Wedge Defects OFL, PFL, ITL, Dorsal Vertex

Diagnostic Points

- Most dementing illnesses are global brain disorders
- Each has its own pattern
- There is partial overlap among them
- The patterns have diagnostic utility
- NN can distinguish these patterns
- Amyloid imaging may play an auxiliary role

Greatest Benefit of NN in MCI & Dementia

- Memory impairment - early diagnosis
- Mild Cognitive Impairment – early & differential diagnosis
- Possible (NINCDS-ADRDA) Alzheimer's dz - differential diagnosis
- Mild probable (NINCDS-ADRDA) Alzheimer's dz- differential diagnosis

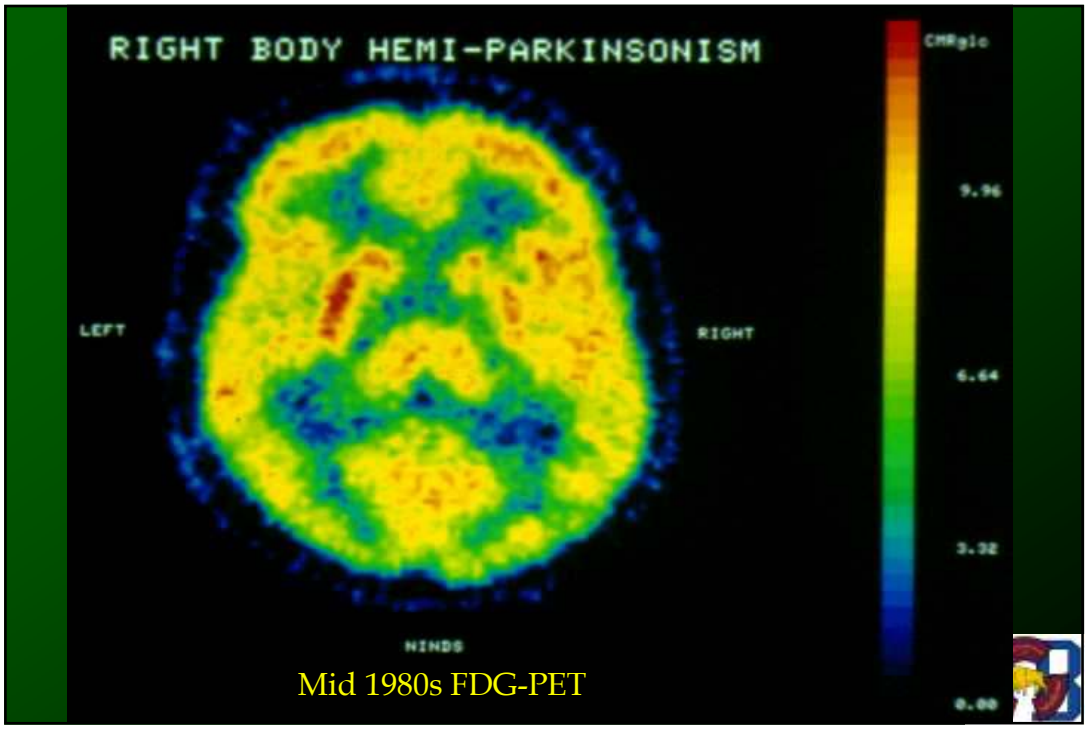
Parkinsonism: Parkinson's disease, Other disease

Differential Diagnosis of Parkinsonism

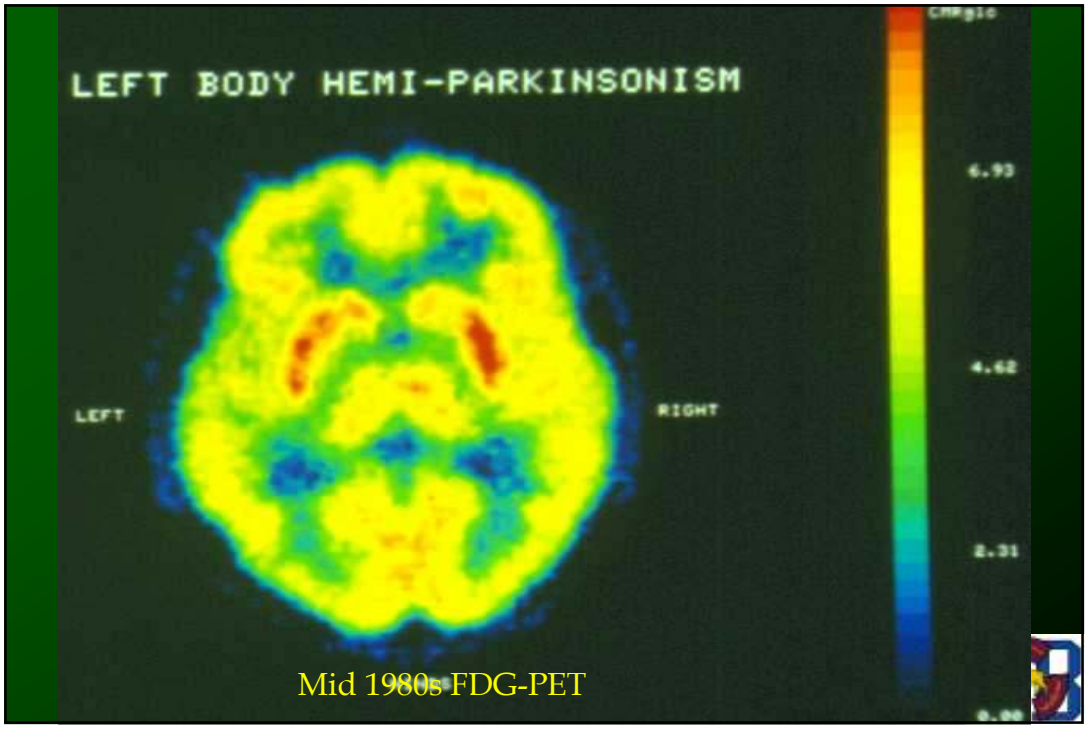
- Lewy body disorders: IPD, DLB
- Atypical parkinsonian syndromes: MSA, PSP, CBD, FTD (TDP-43)
- Secondary parkinsonian syndromes: Vascular dz, drugs, NPH
- Essential tremor

Differential Diagnosis of Parkinsonism

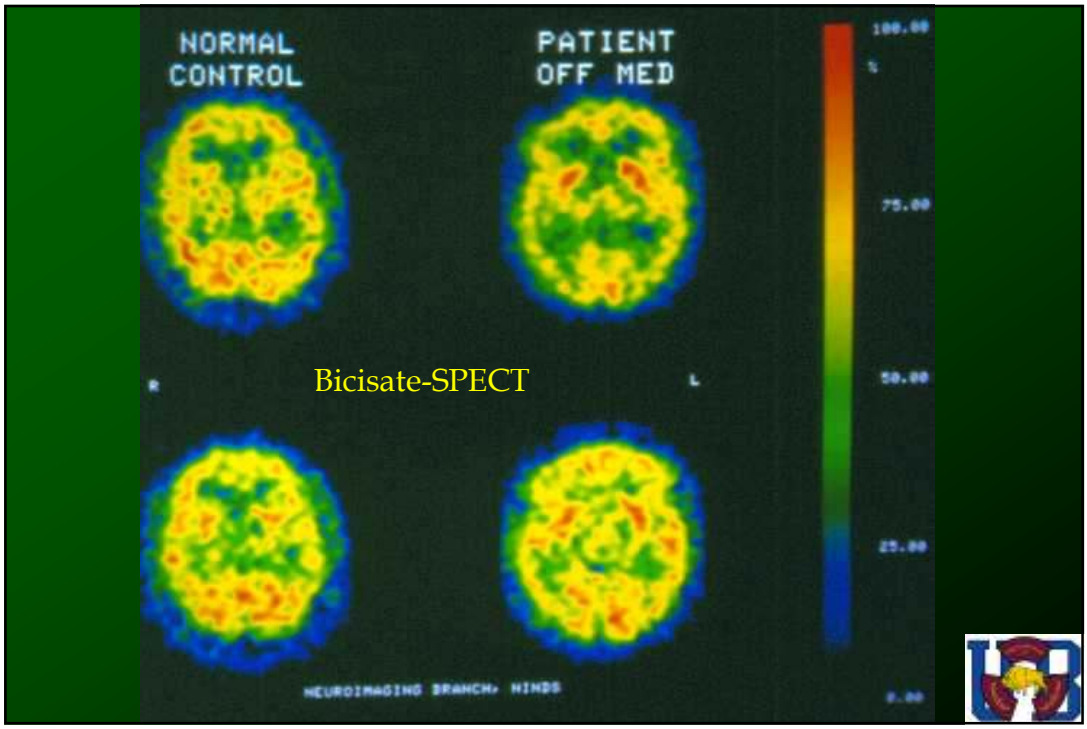
- IPD: Idiopathic Parkinson's Dz
- DLB: Dementia with Lewy Bodies
- MSA: Multiple System Atrophy
- PSP: Progressive Supranuclear Palsy
- CBD: Corticobasal Degeneration
- FTD: Frontotemporal Dementia
- NPH: Normal Pressure Hydrocephalus

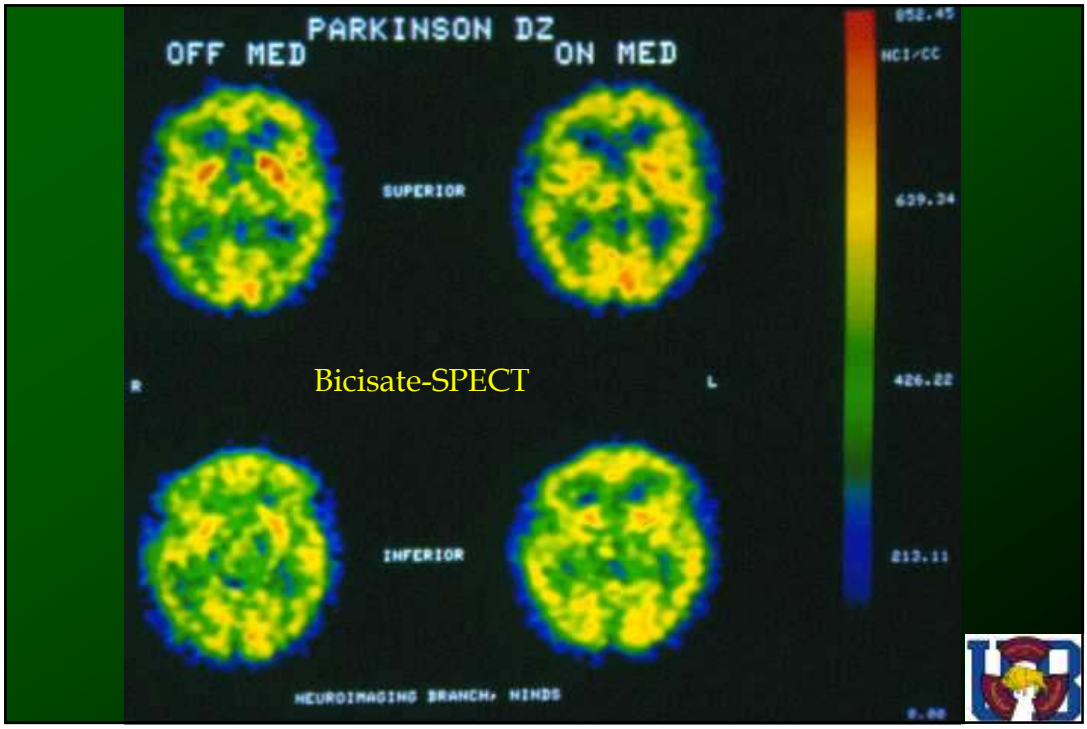


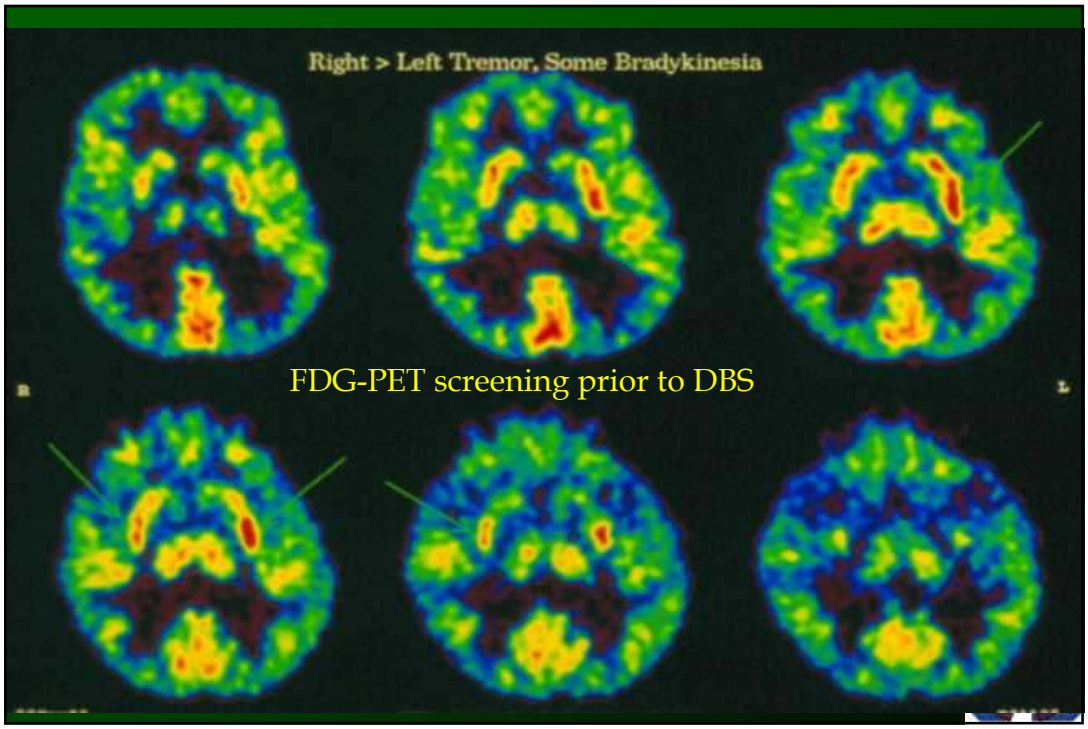
Mid 1980s FDG-PET

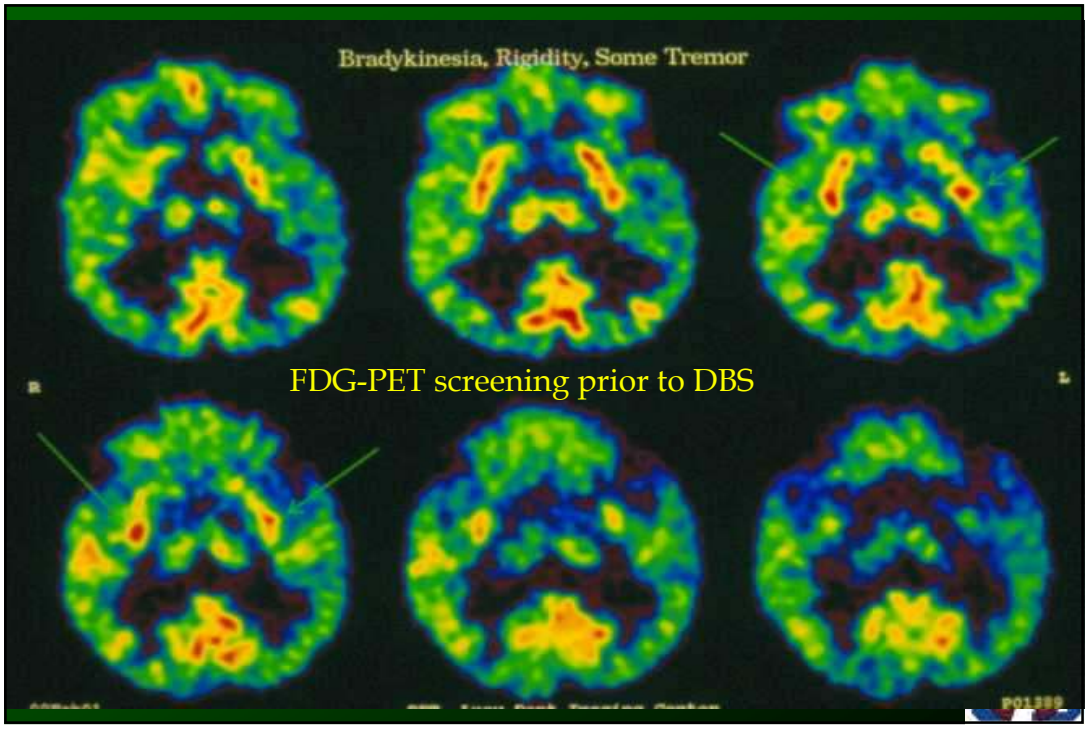


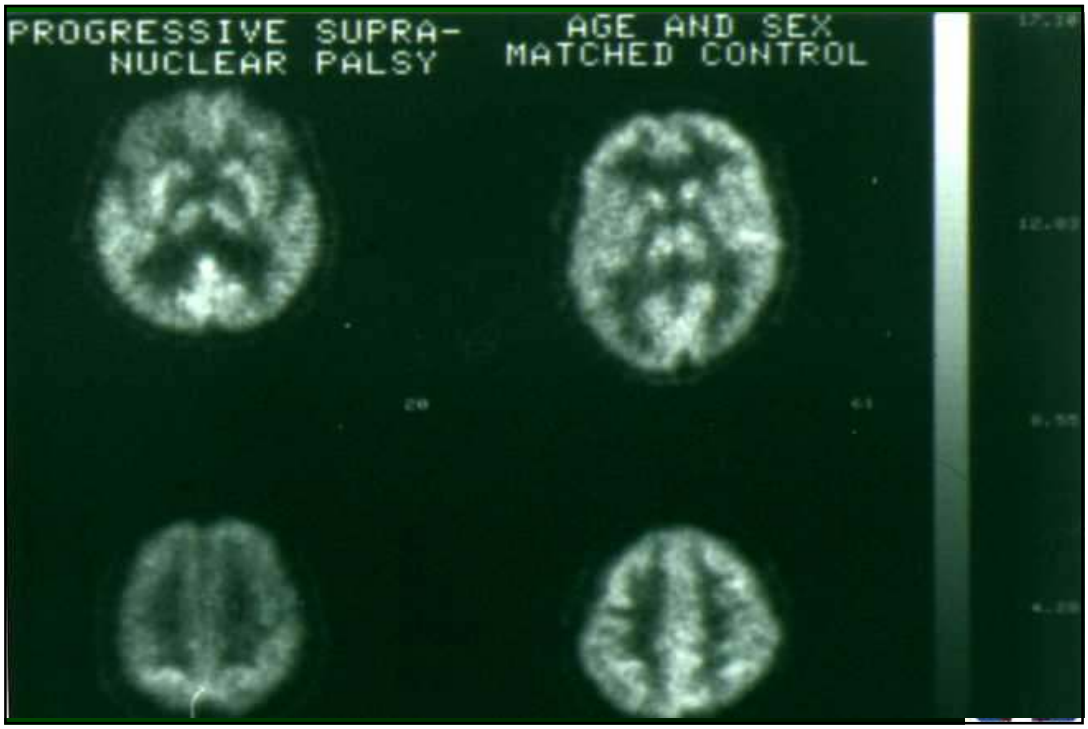
Mid 1980s FDG-PET

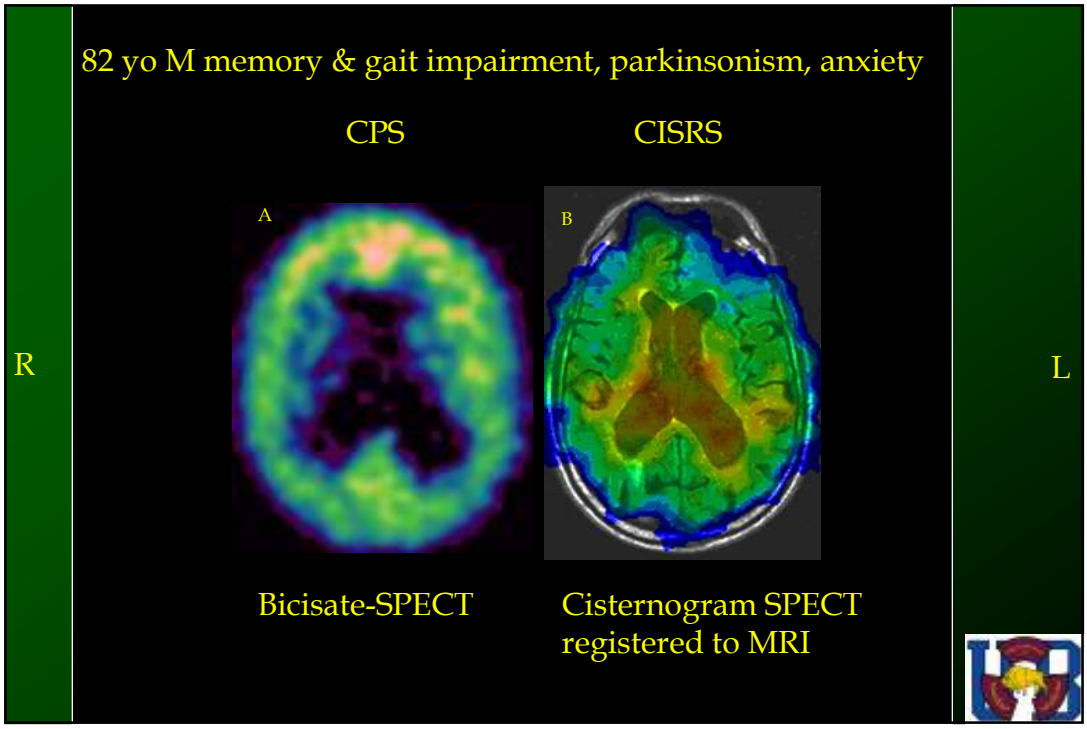

NORMAL
CONTROL
PATIENT
OFF MED
Bicisate-SPECT
NEUROIMAGING BRANCH, NINDS


PARKINSON DZ
OFF MED
ON MED
SUPERIOR
Bicisate-SPECT
INFERIOR
NEUROIMAGING BRANCH, NINDS

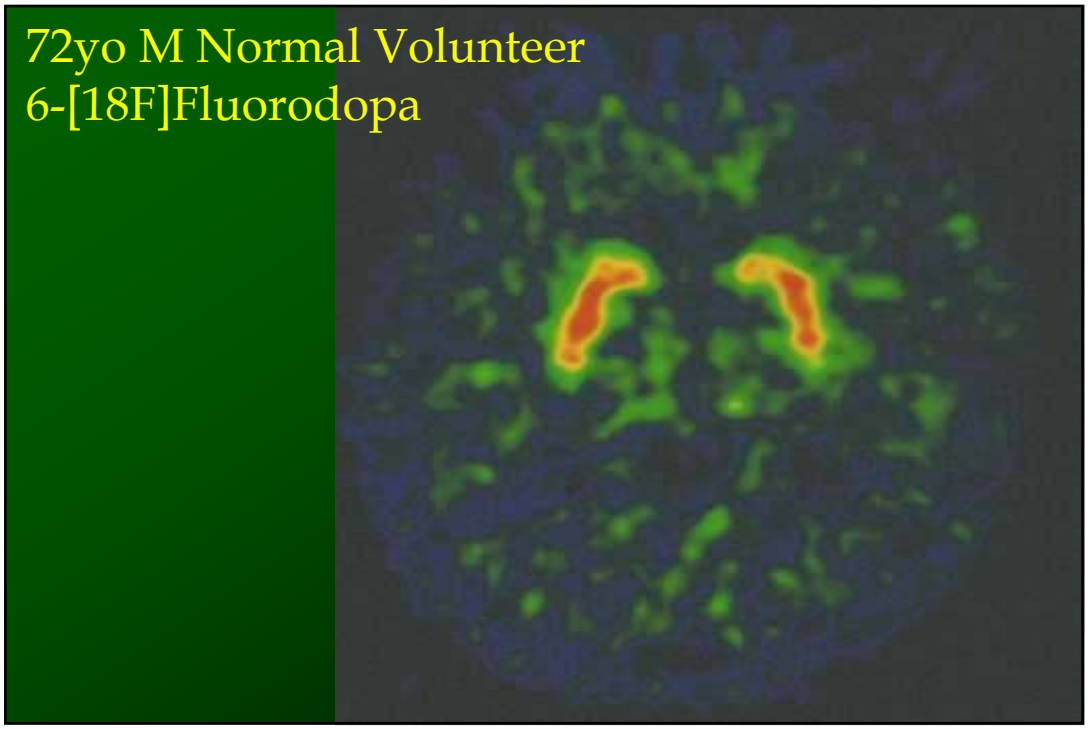

Right > Left Tremor, Some Bradykinesia
FDG-PET screening prior to DBS


Bradykinesia, Rigidity, Some Tremor
FDG-PET screening prior to DBS

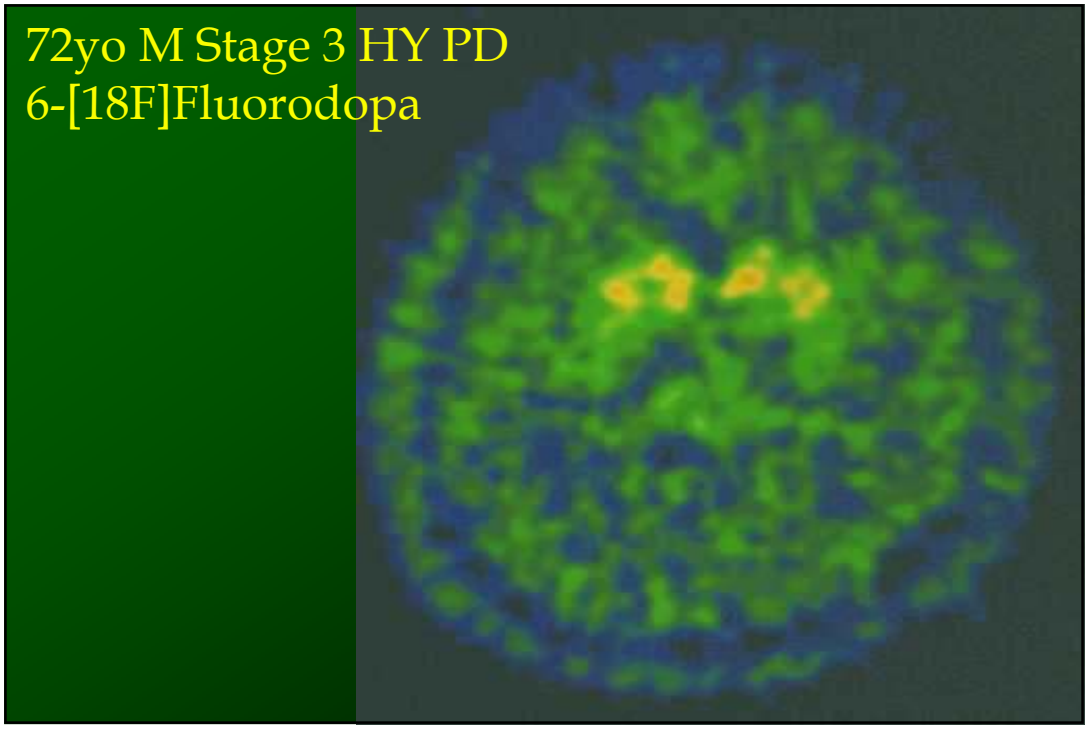

PROGRESSIVE SUPRA-
NUCLEAR PALSY
AGE AND SEX
MATCHED CONTROL


82 yo M memory & gait impairment, parkinsonism, anxiety
CPS
CISRS
A
B
R
L
Bicisate-SPECT
Cisternogram SPECT
registered to MRI

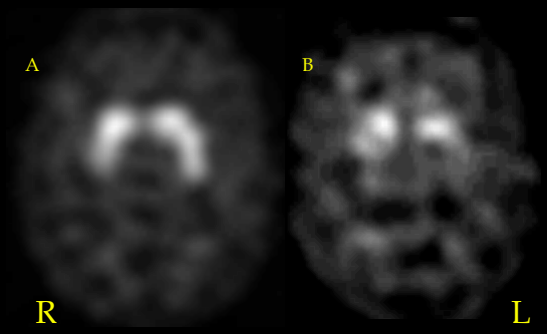
72yo M Normal Volunteer
6-[18F]Fluorodopa



72yo M Stage 3 HY PD
6-[18F]Fluorodopa



DaTscan, ie. Ioflupane I 123: 2 Tremor Patients



Normal

Neurodegenerative Parkinsonism, likely Parkinson's Disease

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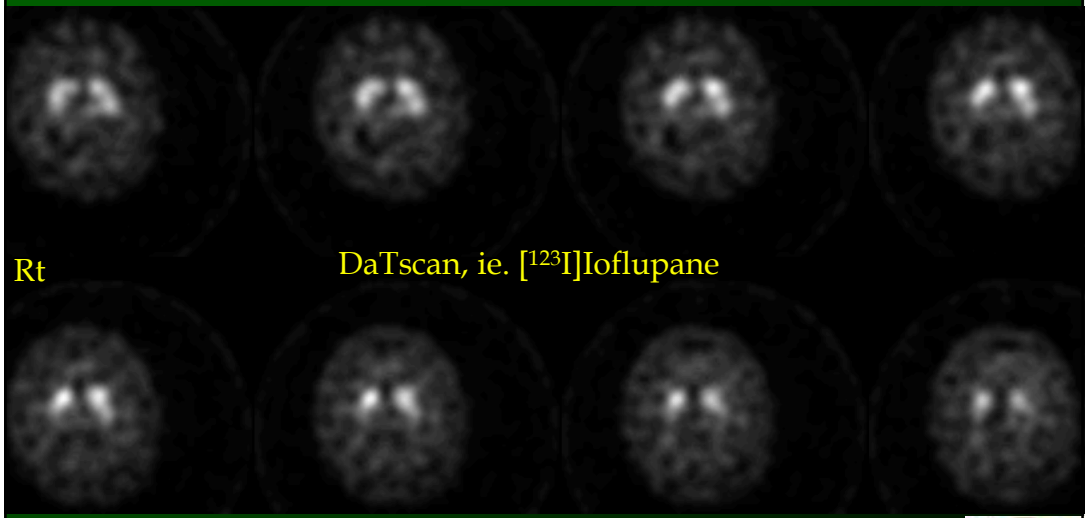
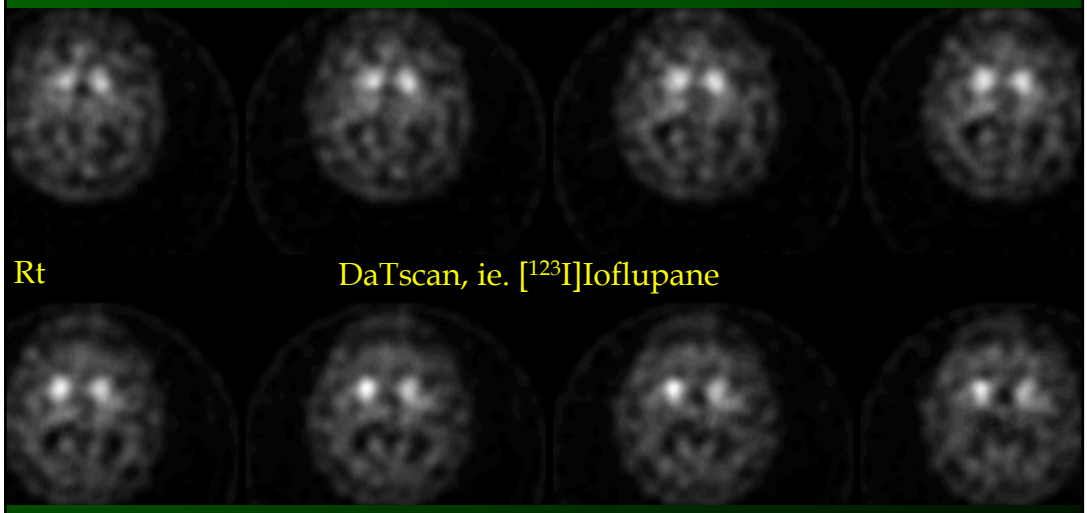
Asymmetric Parkinsonism, Lt>Rt, Psychiatric Patient



Early Parkinson's Disease: Rt. Posterior putamen worst

73 yoM with tremors, rigidity, festination



Posterior putamen worse anterior putamen worse than caudate
C/W advanced stage idiopathic Parkinson's disease

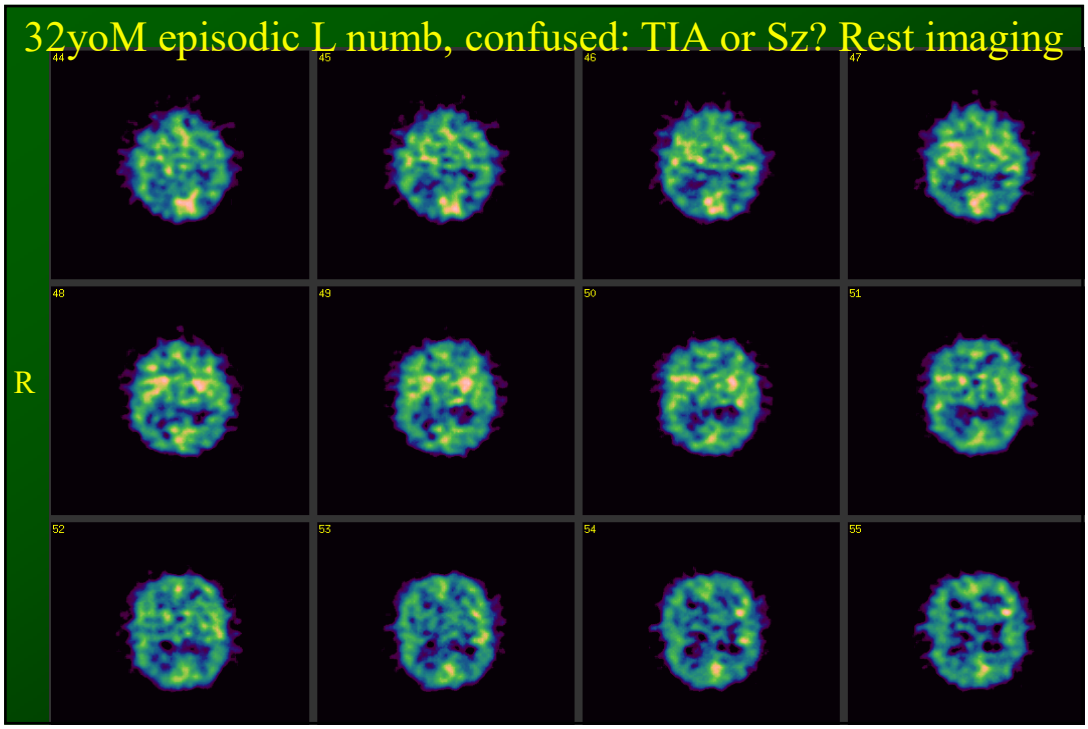
Limitations of DaTscan

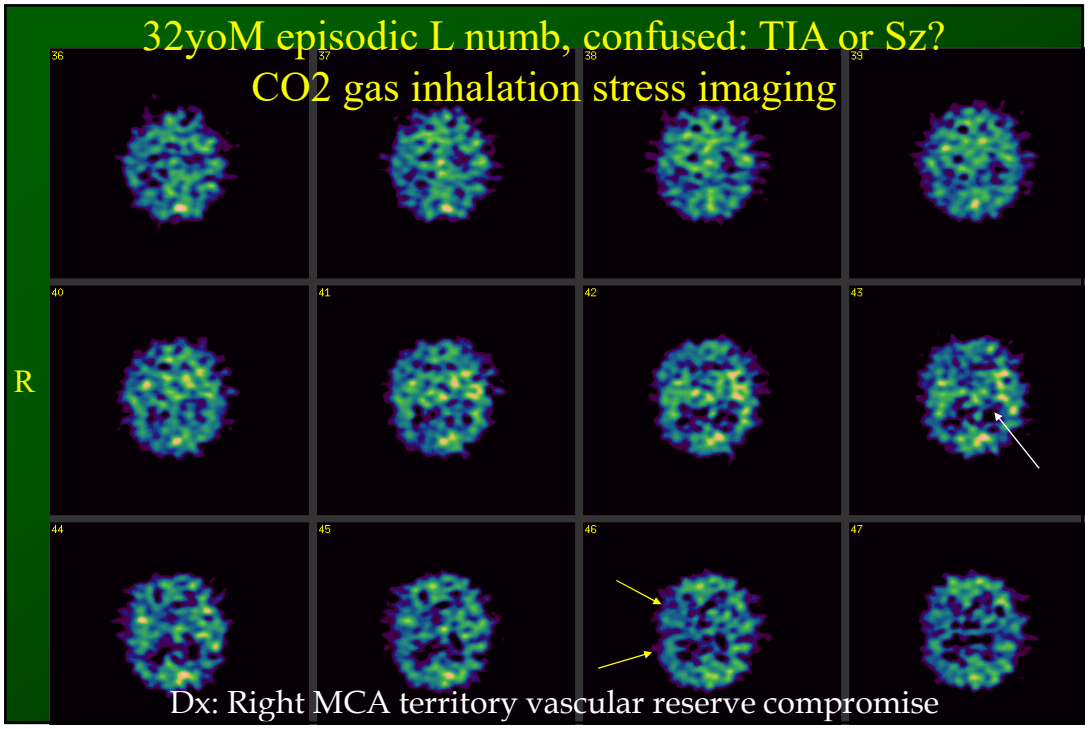
- Differential Diagnosis is not definitive
- Cannot distinguish between different neurodegenerative disease
- FTLD can be normal
- NPH can be abnormal
- Many drugs can confound interpretation
- Striatal DA denervation is only thing DaTscan shows

Greatest Benefit of NN in Parkinsonism

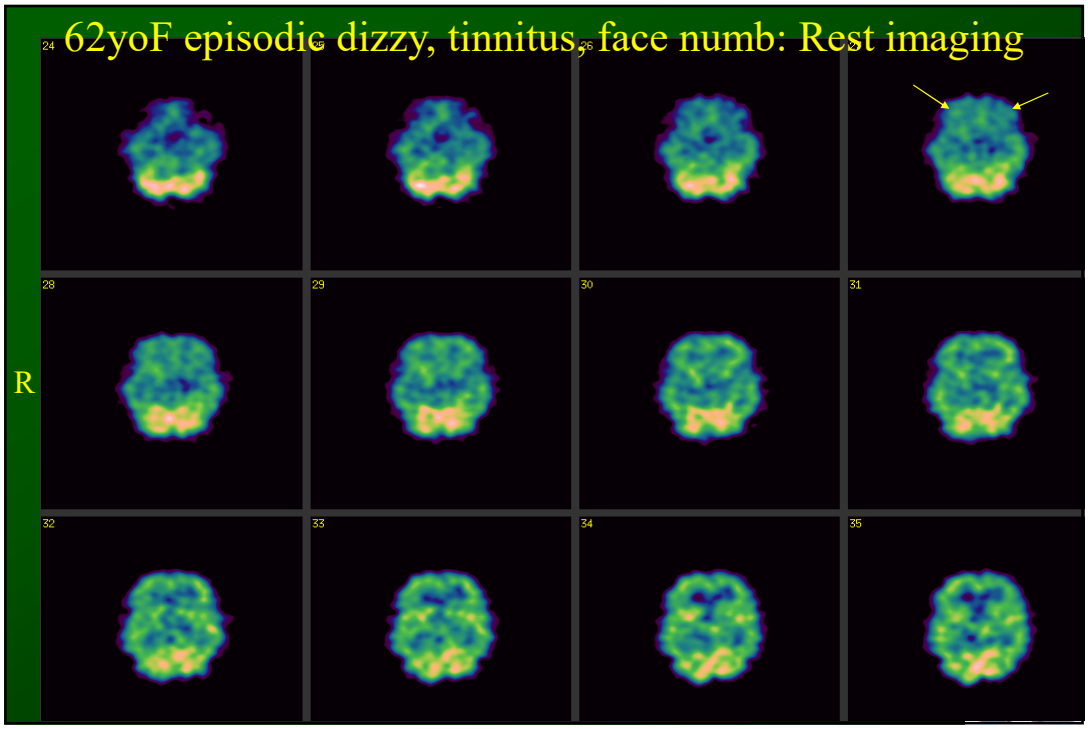
- Early diagnosis
- Differential diagnosis

Epilepsy: Episodic Neurologic Syndromes Diagnosis, Pre-Surgical Planning

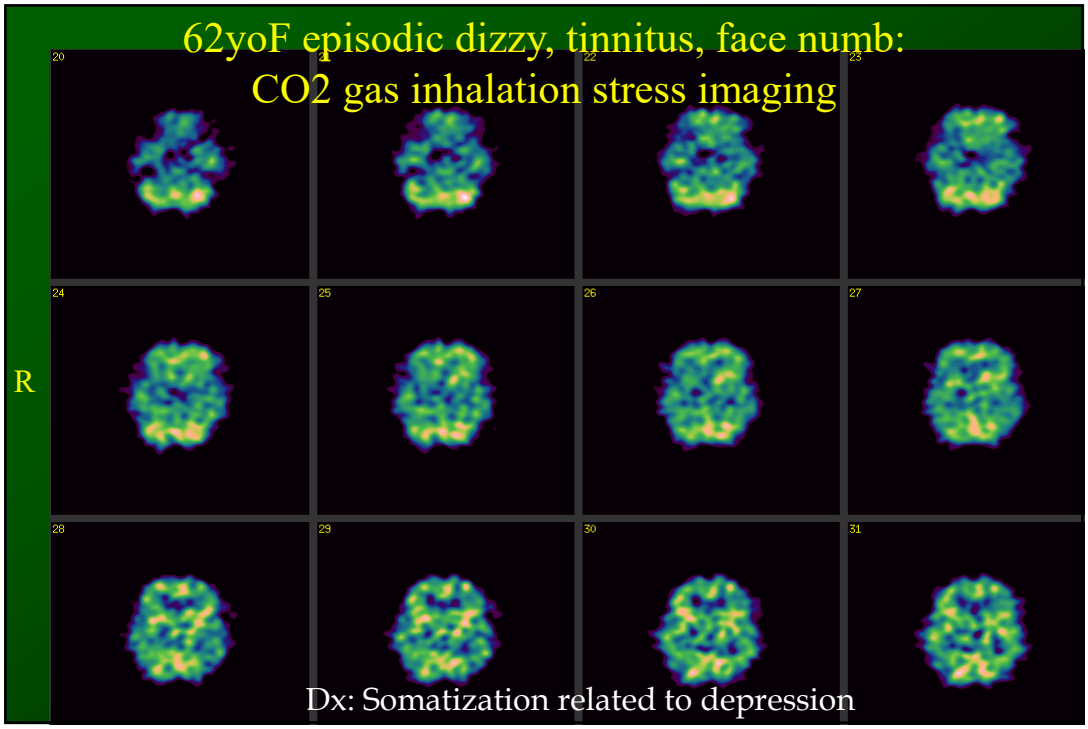

32yoM episodic L numb, confused: TIA or Sz? Rest imaging
R


32yoM episodic L numb, confused: TIA or Sz?
CO2 gas inhalation stress imaging
R
Dx: Right MCA territory vascular reserve compromise

62yoF episodic dizzy, tinnitus, face numb: Rest imaging



62yoF episodic dizzy, tinnitus, face numb: CO2 gas inhalation stress imaging

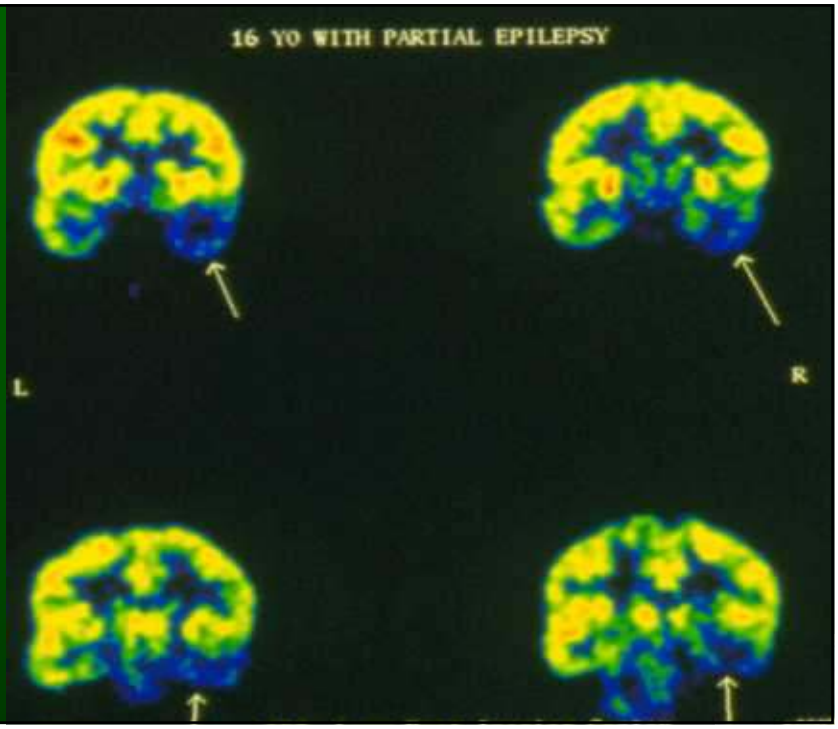


Dx: Somatization related to depression

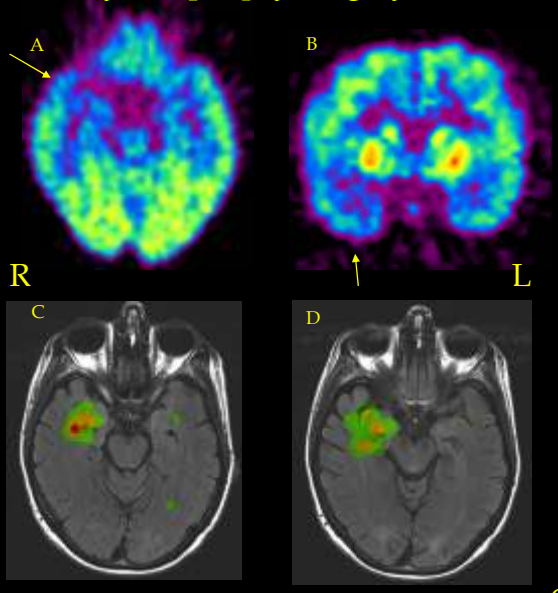
16 yo M with onset of refractory epilepsy at 12 yo

Epilepsy

Epilepsy



54 yo F epilepsy surgery candidate



FDG-PET

RESIST: Registered subtraction ictal SPECT

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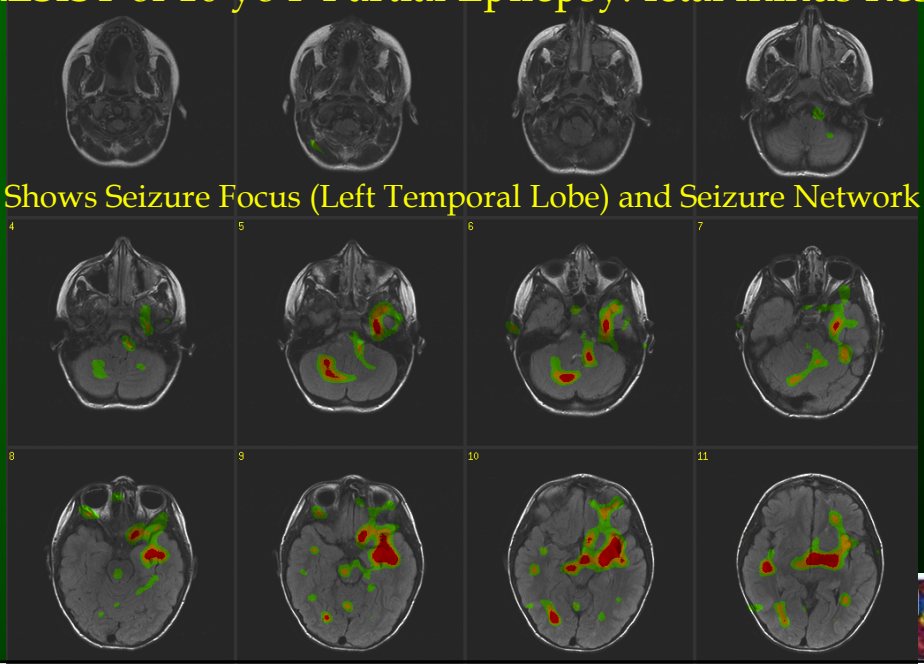
RESIST of 10 yo F Partial Epilepsy: Ictal minus Rest

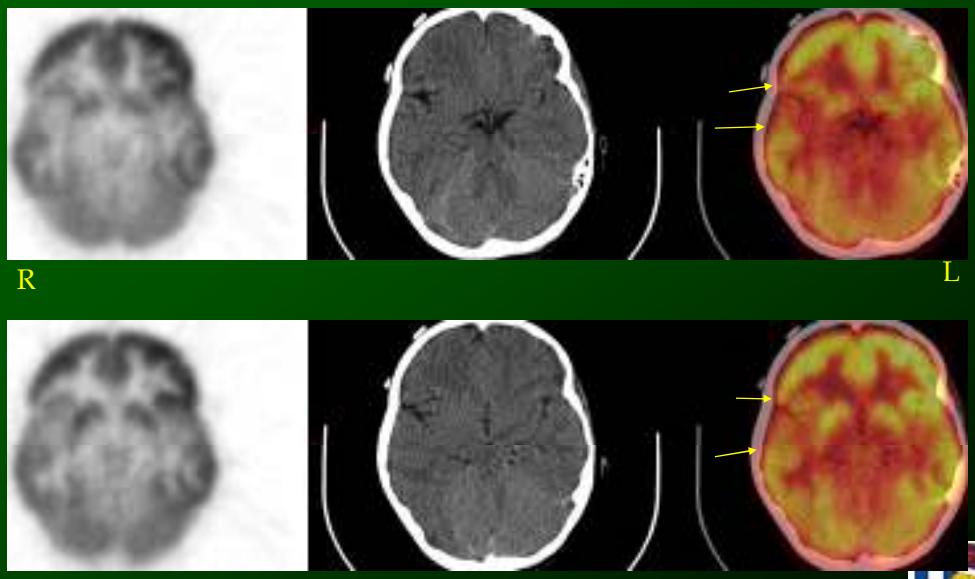


Shows Seizure Focus (Left Temporal Lobe) and Seizure Network

R

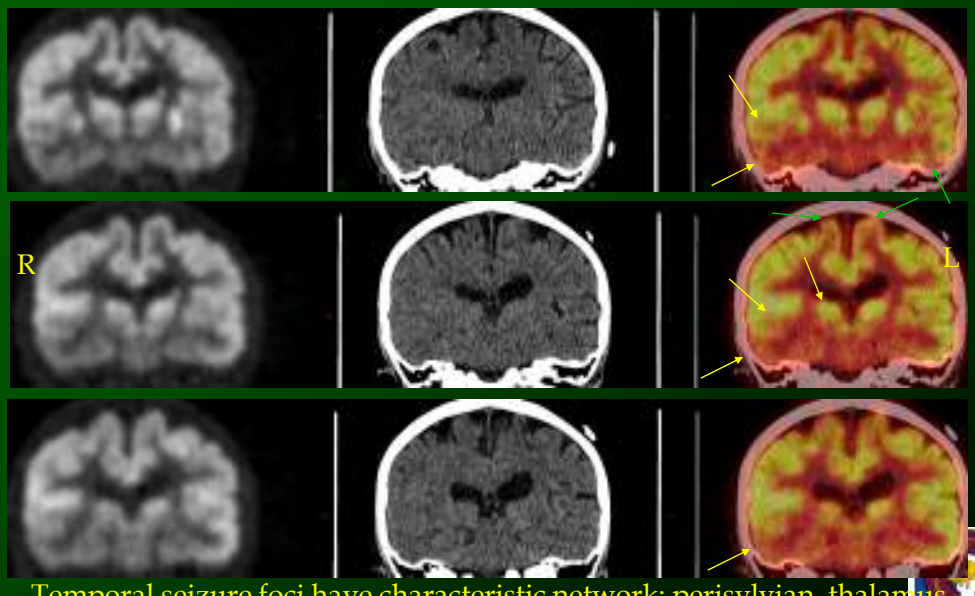
L

8 yo M with refractory epilepsy



Worst hypometabolism is in frontal operculum

18 yo F with refractory complex partial epilepsy



Temporal seizure foci have characteristic network: perisylvian, thalamus

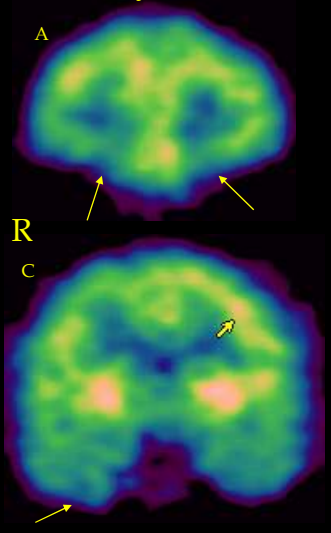
Greatest Benefit of NN in Epilepsy

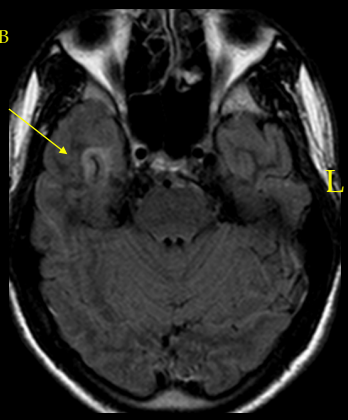
- Diagnose episodic neurologic syndromes
- Localize seizure focus in partial epilepsy
- Lateralize seizure focus in partial epilepsy
- Identify focal vs. multifocal vs. diffuse disease

NN shows at the seizure focus:
-hypofunction inter-ictally
-hyperfunction ictally

Traumatic Brain Injury: Mild TBI; Post-Concussive Syndrome; Is this a 2ndary gain?

22 yo M with 1.5 yr H/O mood and cognitive impairment after MVA





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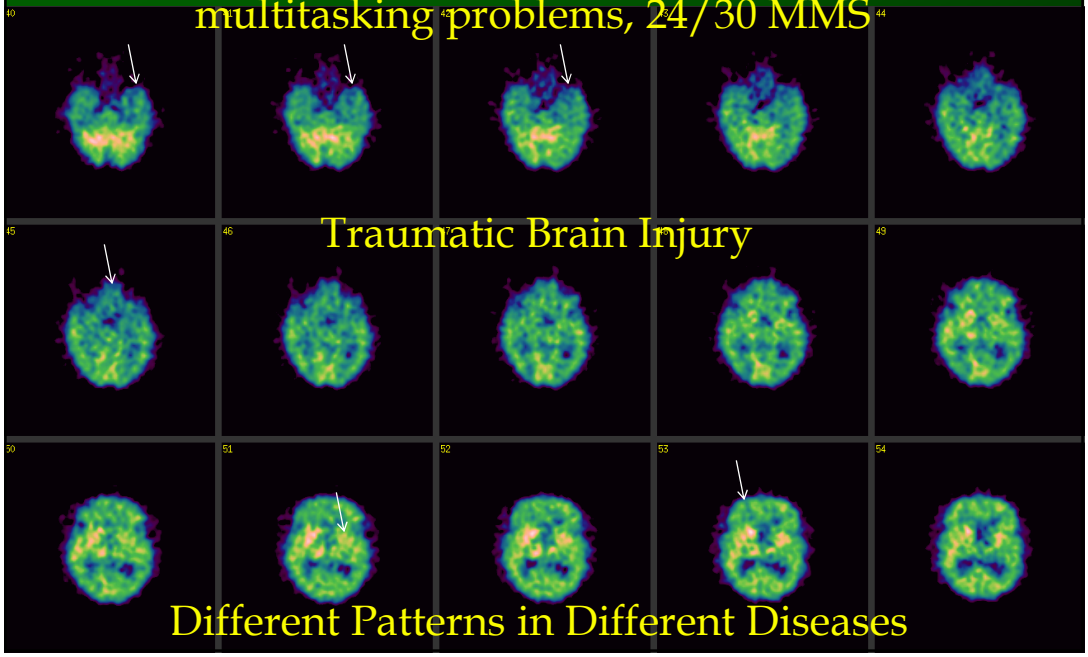
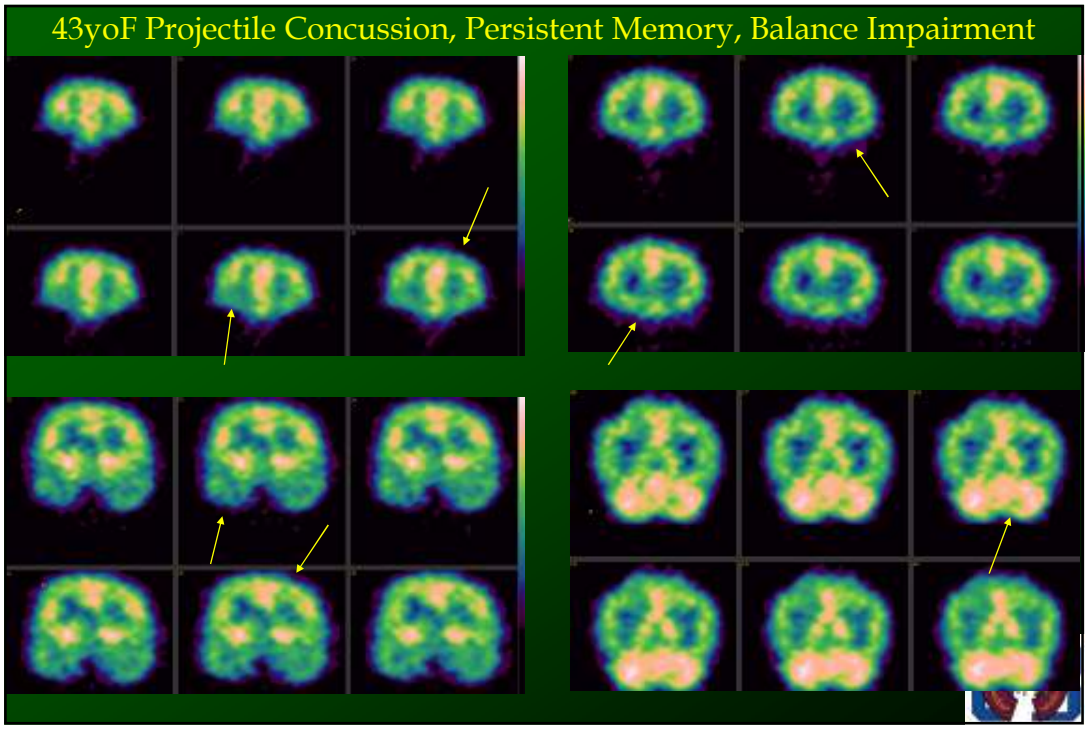
Traumatic Brain Injury

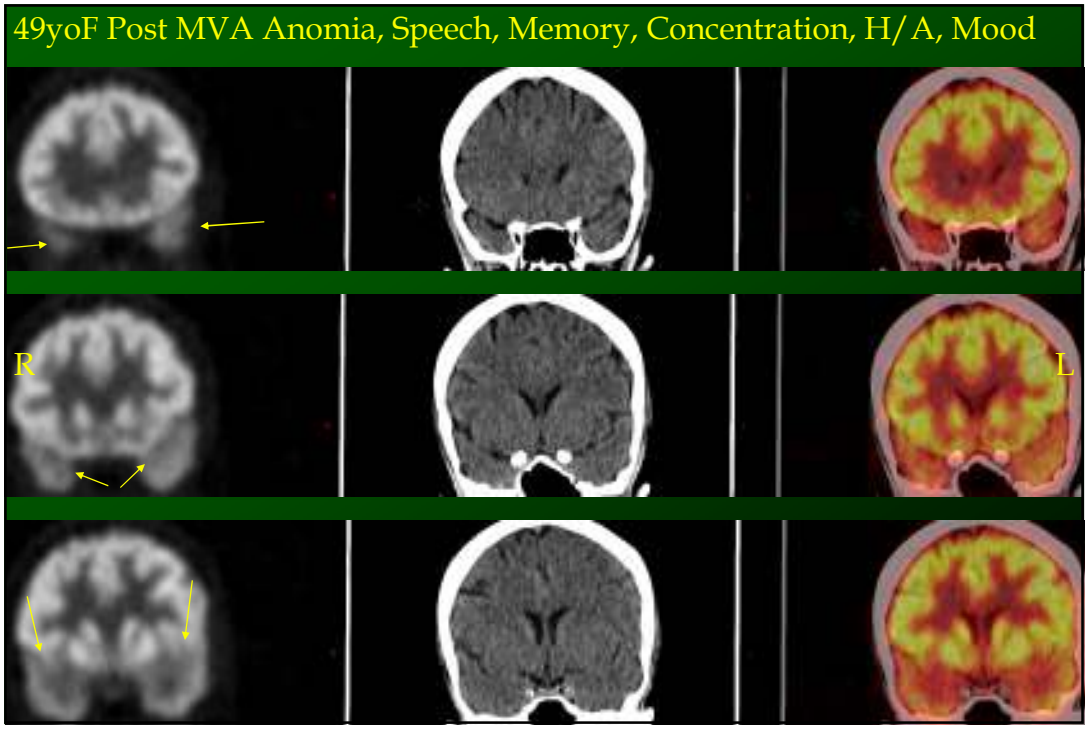
70yoM MVA 10 mo ago, memory, multitasking problems, 24/30 MMS

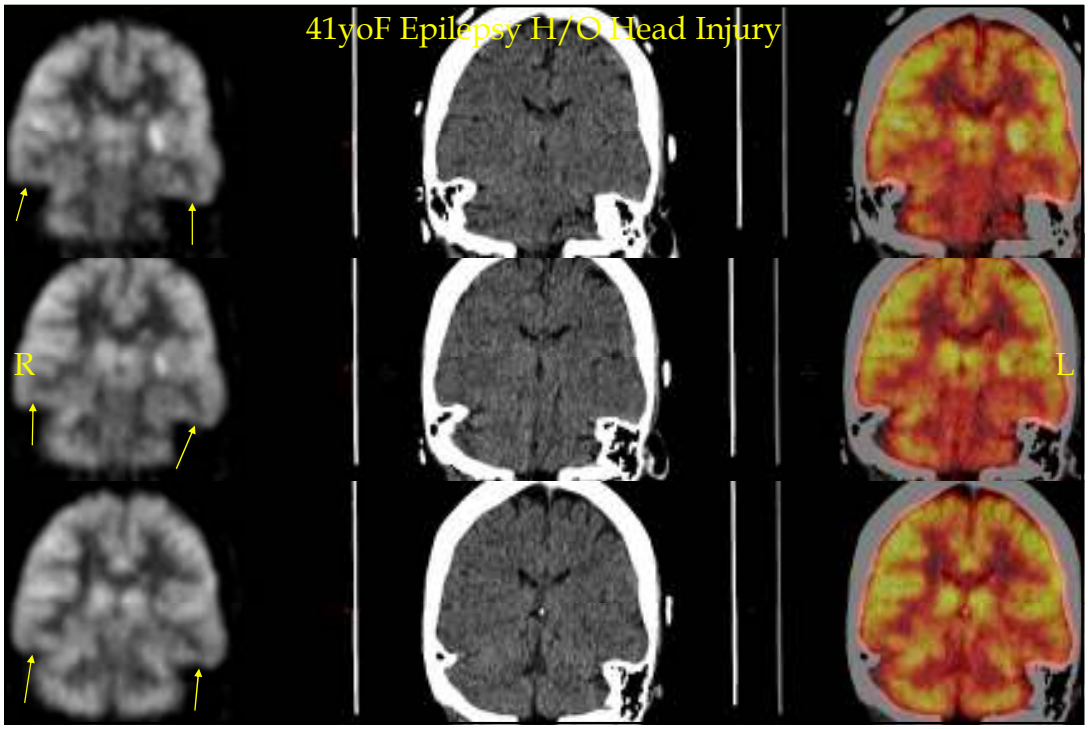


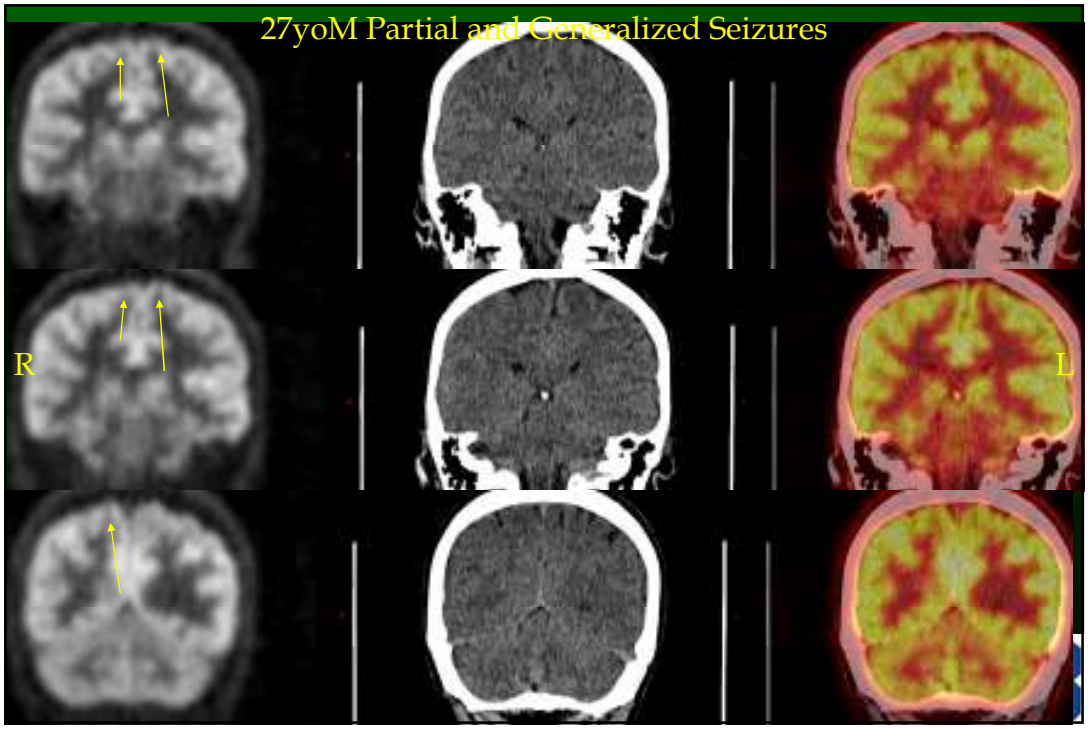
Traumatic Brain Injury

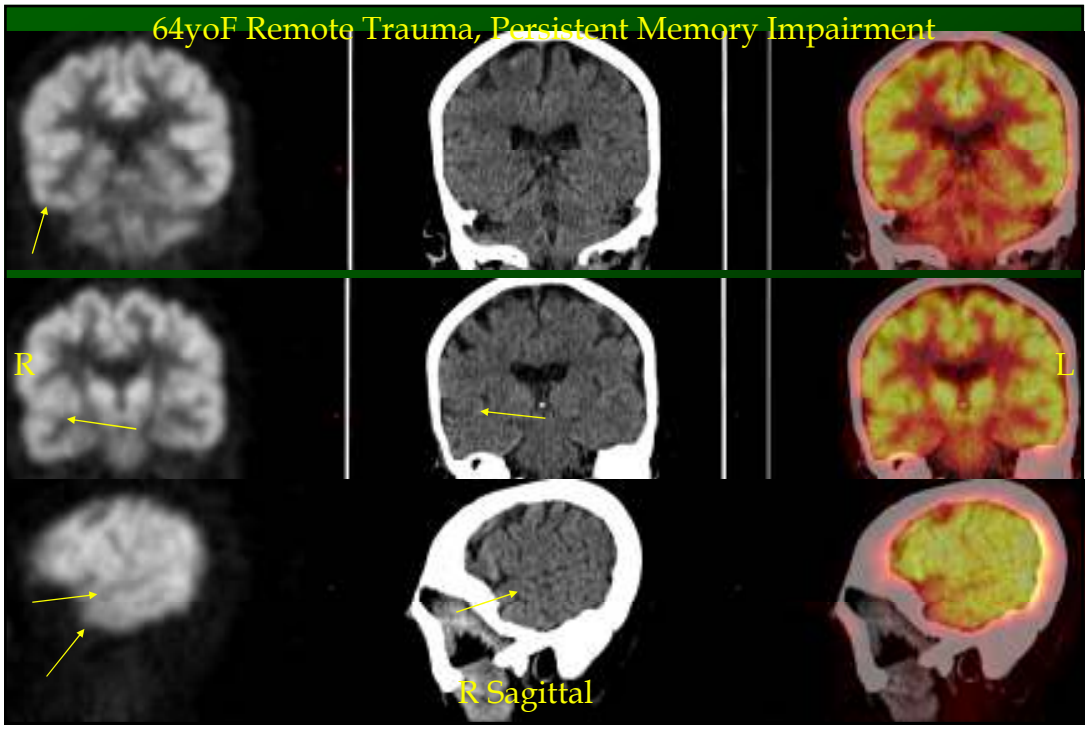
Different Patterns in Different Diseases


43yoF Projectile Concussion, Persistent Memory, Balance Impairment


49yoF Post MVA Anomia, Speech, Memory, Concentration, H/A, Mood
R
L


41yoF Epilepsy H/O Head Injury
R
L


27yoM Partial and Generalized Seizures
R
L



NN Findings in Mild TBI

- Regional or wedge defects of cortex in the absence of CT or MRI abnormalities
- Typical regions: polar frontal, orbital frontal, polar temporal, inferior temporal, parasagittal dorsal frontal, parasagittal dorsal parietal, inferior cerebellum

Greatest Benefit of NN in Mild TBI

- Normal MRI in symptomatic patient in acute or chronic phase
- Postconcussive Syndrome

Nuclear Neurology Visual Read Primer

- This involves pattern recognition
- Disease processes have different regional predilections
- The regional function profile is the pattern
- Establish regional assessment routine so all brain structures get included in the pattern
- Establish comparison structures: pons, calcarine cortex, other primary cortex, contralateral homologous structure, cranial soft tissue
- Relate NN findings to clinical presentation and to clinical questions

Nuclear Neurology
Visual Read Challenges

- There is pattern overlap between different disease states
- Patterns evolve in progressive disorders
- There are different subpatterns within each disease
- Comorbidity is the rule in the real world

A new type of clinical brain imaging: nuclear neurology

By Robert S. Miletich

Much of the historical development of medical imaging after the time of Wilhelm Rontgen was fueled by a quest for an image of the brain.

agnostic accuracy of NN directly results from this characteristic of measuring physiology through both molecular and cellular imaging.

Diagnosis of neurologic syndromes is particularly difficult because it is a two-step process. First, any particular set of neurologic signs and symptoms can be due to pathology at multiple sites in the nervous system.

There are two general class
ams, separated by the type o
process measured, what I call b
cific physiology. Basal physiol
those processes which all cells
engage in. All cells require inte
tabolism in order to generate s
All cells need blood perfusion fo

We are now entering into a new era, wherein we clinically have the capability of creating images of the functioning brain. This is the focus of nuclear neurology, a 21st century diagnostic field now available for clinical medicine.

Share this story: dotmed.com/news/37256

Requirements for Nuclear Neurology

- Professional: Training
- Professional: Certification
- Professional: Authorized User on RML
- Center: Staffing, Equipment
- Center: Accreditation from ACR or IAC
- Center: Radioactive Materials License(RML)
- Center: Insurance Accreditation
- Business: Payers
- Business: Customers

Nuclear Neurology Regulations

- Nuclear Regulatory Commission (NRC)
- NRC or States regulate: 37 Agreement States
- RML specifies what radioisotopes & quantities
- To supervise and interpret nuclear studies, you must be an Authorized User (AU) on the RML
- To be AU, you need government-recognized appropriate training and experience
- Training is in Title 10 Code of Federal Regulations Subpart 35.290

10 CFR 35.290 Board Path

- Certification by Medical Specialty Board
- 700 hours of training and experience in radionuclide handling and safety in medical use of unsealed byproduct material
- Pass an exam in radiation safety, radionuclide handling, quality control
- American Board of Nuclear Medicine
- American Board of Radiology
- Osteopathic equivalents of 2 above
- Certification Board of Nuclear Cardiology

10 CFR 35.290 Attestation Path

- Preceptor Authorized User attests to:
- 700 hours of training and experience in radionuclide handling and safety in medical use of unsealed byproduct material
- 80 hours of classroom and laboratory training
- Requirements are exactly the same as the Board path
- This path may not be available in all states

10 CFR 35.290 Didactic Training

- 80 hours of classroom and lab training in:
- Radiation physics and instrumentation
- Radiation protection
- Mathematics of radioactivity
- Chemistry of byproduct material for medical use
- Radiation biology

10 CFR 35.290 Work Experience

- 700 Hours Supervision by an Authorized User:
- Handling radioactive materials, surveys
- Quality control of equipment
- Human subject dosages quality control
- Administrative controls to prevent medical events from unsealed byproduct material
- Safely contain radioactive material spills and decontamination
- Administering radioactive drugs
- Quality control and eluting generators

TRAINING AND CERTIFICATION

5 TRAINING PATHWAYS: Have existed since 2010.

PATHWAY	REQUIREMENT	DURATION(YR)	ABMS BOARD
1	1yr. Internship	3	ABNM
2	Clinical. BE/BC	2	ABNM
3	DR	1 (16 mo total)	ABR, ABNM
4	In DR Residency	4 (16 mo total)	ABR, ABNM Poss.
5*	In DR Residency	5 (>16 mo total)	ABR, ABNM Poss.

*Pathway 5 is only at Stanford and John Hopkins currently.

Nuclear Neurology Training

- 1-2 Year Fellowship
- ABNM Board Certification: 2 years training for diplomates of ABPN
- I am in the process of forming a fellowship at University at Buffalo to meet the 10 CFR 35.290 requirements
- ASN can function as clearing house of training
- ASN can help establish the Certification Board of Nuclear Neurology