Demencias primarias: claves diagnósticas

Juan Alvarez-Linera Prado

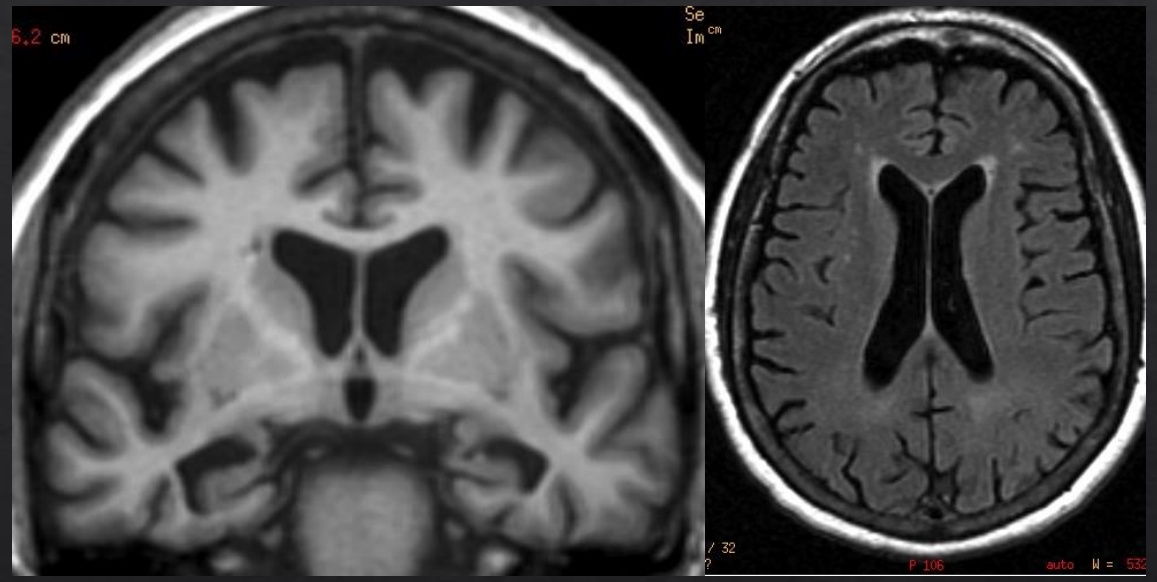
Hospital Ruber Internacional

Demencias primarias

- Enfermedad de Alzheimer
- Demencia con cuerpos de Lewy
- Demencia frontotemporal
- Demencia en otras enf. Degenerativas
  - PSP/Degeneración cortico-basal
  - Atrofia Multisistema
  - Huntington
  - Enfermedades priónicas

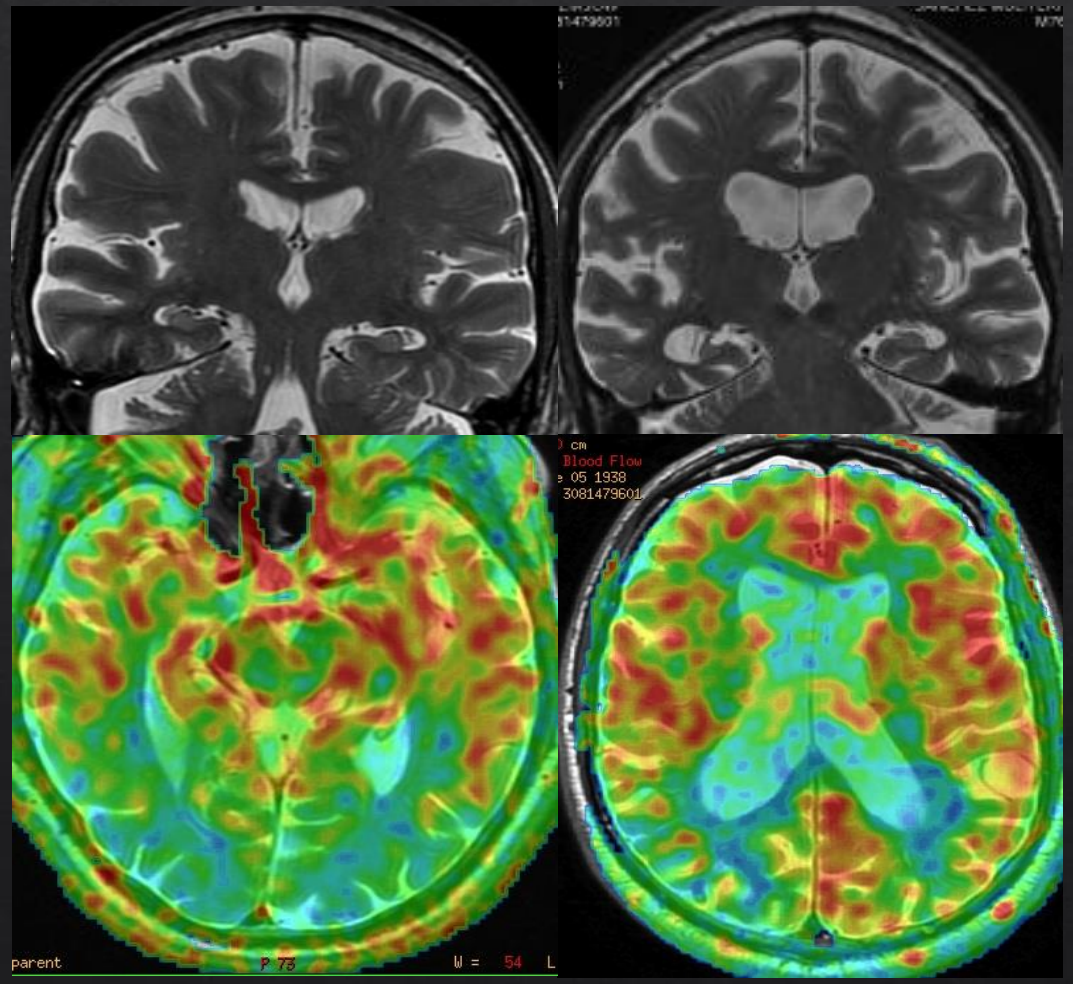
Enfermedad de Alzheimer

- Principal causa de demencia
- Frecuentemente asociada a otras
  - Vascular
  - Parkinson
- Atrofia temporal medial simétrica
- Depósito de Amiloide



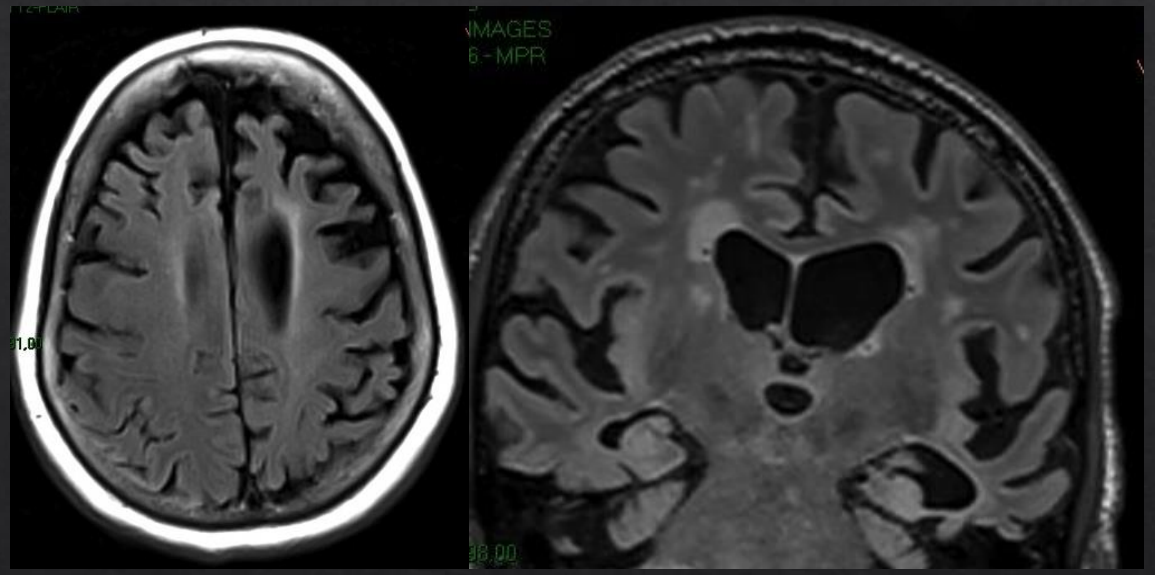
Demencia con cuerpos de Lewy

- Segunda enfermedad neurodegenerativa
- Demencia y Parkinson
- Hipofunción posterior (alucinaciones)
- DAT-scan +
- Alteración en sustancia negra
  - Nigrosoma I
  - Neuromelanina



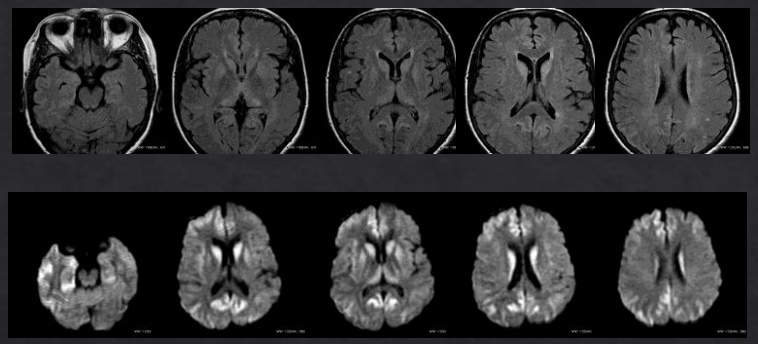
Demencia frontotemporal

- Importante causa de demencia en edad temprana
- Alteraciones de conducta como rasgo principal
- Atrofia anterior asimétrica frecuente
- No acumula amiloide



Demencia en otras enf. neurodegenerativas

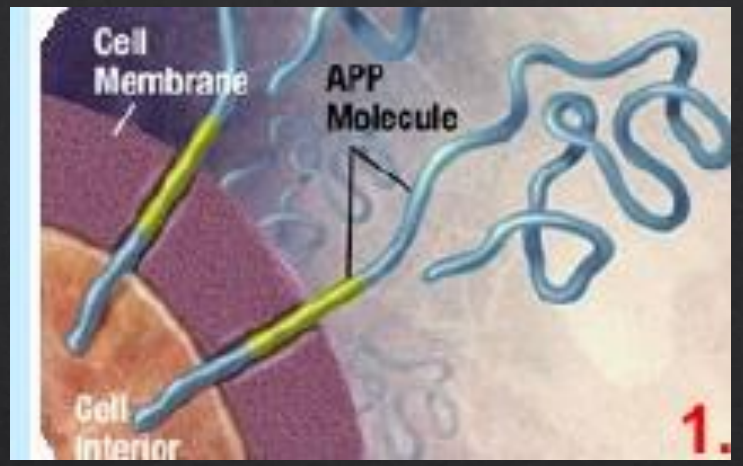
- Diagnóstico clínico, confirmación AP
  - Excepción: CJD (secuencias de difusión)
- Neuroimagen: escaso papel
- Ocasionalmente hallazgos característicos (tardíos)
  - PSP: mesencéfalo
  - MSA: putamen (MSA-p), protuberancia(MSA-c)
  - Huntington: estriado

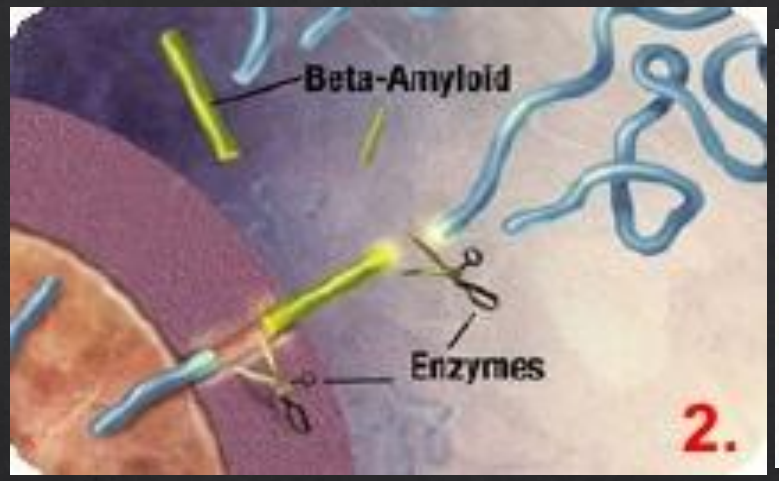


Enfermedad de Alzheimer (EA)

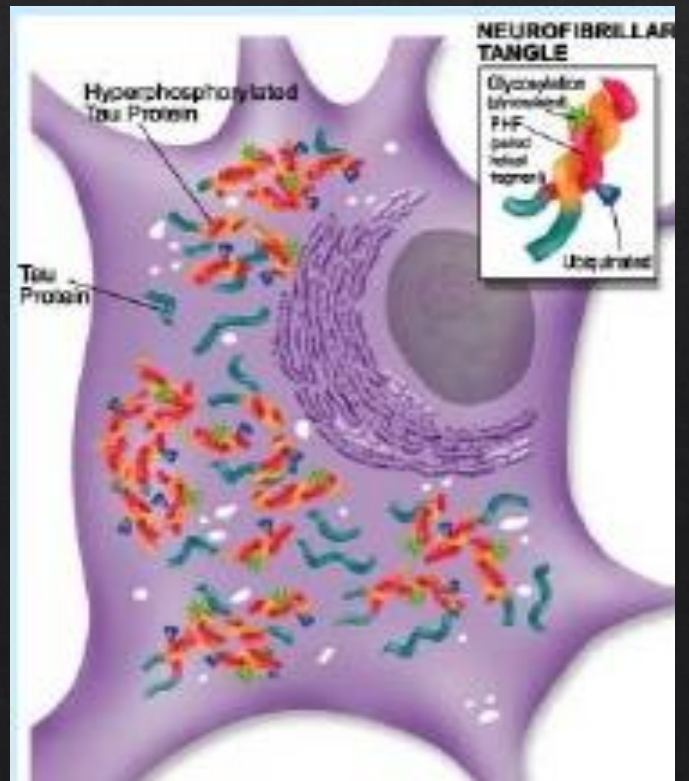
- Causa más frecuente de Demencia (60-70%) en países desarrollados. Predominio en mujeres (1.6:1)
- La mayoría: casos esporádicos tardíos (>65a)
- <5% genéticas: mutaciones APP y Presenilina 1-2
- HAY Tto modificador (Lecanemab). Nuevos ensayos en MARCHA
  - Requiere Dx PRECOZ: marcadores (LCR, Imagen)
  - Requiere Dx Diferencial
  - Requiere control (ARIA)

Fisiopatología





- Teoría amiloide
  - Proteína precursora (APP) + secretasa= ⬆ß-Amiloide
  - Péptido insoluble: neurotoxicidad, inflamación (microglía) alteración de MAPT?
- Acúmulo de ß-Amiloide
  - Depósitos extracelulares: **placas**
  - Presente en todos los enfermos
  - No clara correlación con deterioro
- Proteína asociada a MT (MAPT): depósito de Tau hiperfosforilado
  - Deterioro de microtúbulos
  - Disfunción neuronal, apoptosis
  - **Ovillos intracelulares**: correlacionan con deterioro



Concepto Clásico

Diagnóstico

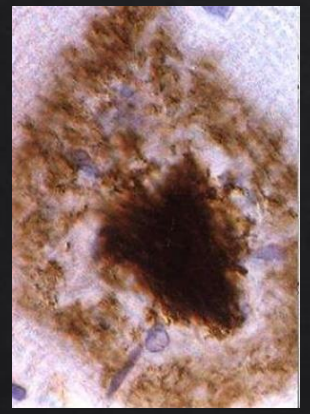
- Clinica
  - Demencia
  - Alteración de memoria
- AP
  - Placas seniles (ß-Amiloide)
  - Ovillos Neurofibrilares

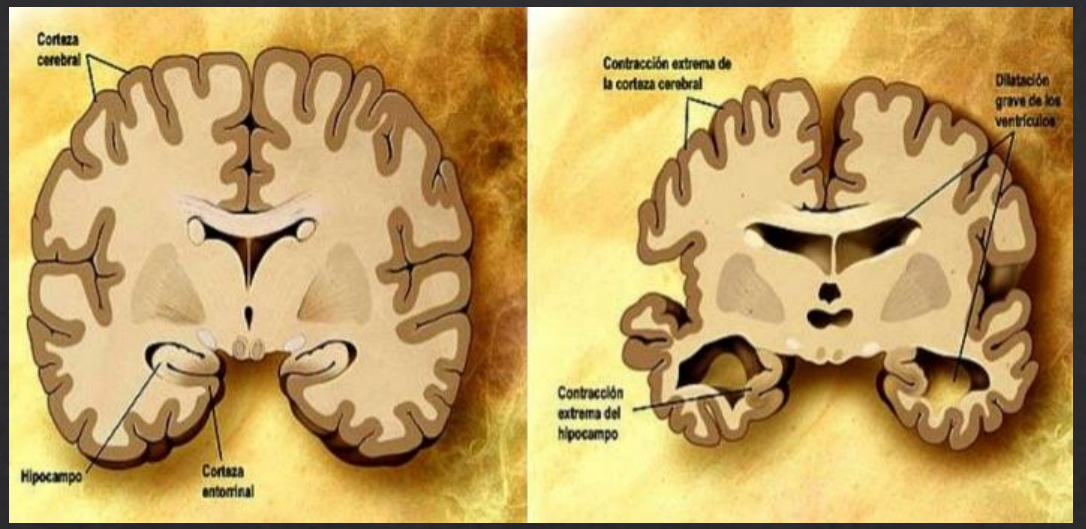
Imagen

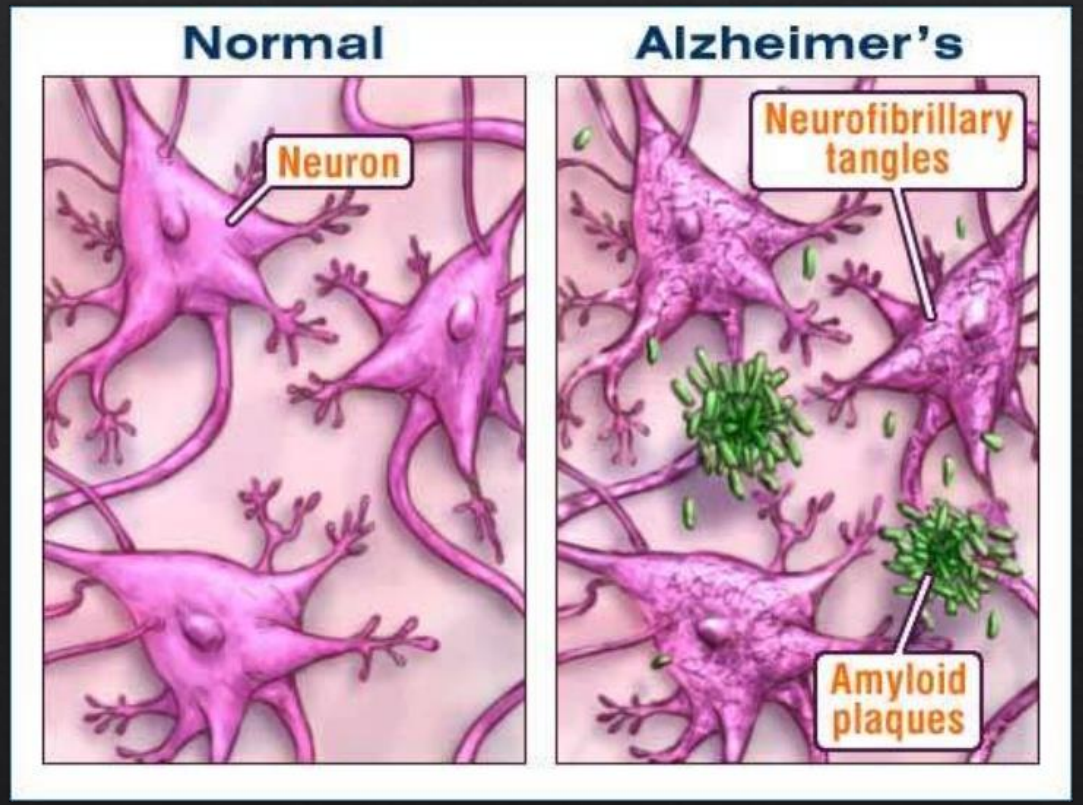
- Descartar causas tratables
- Valorar lesiones vasculares

Anatomía Patológica

- Muerte neuronal progresiva
  - Atrofia cortical
  - Patrón típico (Braak)
    - Hipocampo/Estr. Límbicas
    - Lob. Parietal
- Lesiones características
  - Placas seniles (péptido beta-Amiloide):
  - Ovillos neurofibrilares (Proteína Tau fosforilada)







Cambio de concepto

ANATOMIA PATOLÓGICA

- Debe interpretarse con los datos clínicos
- No existe buena correlación entre deterioro cognitivo y depósitos de beta-amiloide
- Ancianos “resilientes” con patrón AP de EA
- Hay variantes “solo ovillos” y “solo placas”

CLÍNICA

- Diferentes fenotipos
  - Sindrome amnésico
  - Afasia logopénica
  - Degeneración cortical posterior
- Espectro continuo
  - Normal/Quejas de memoria (amiloidosis)
  - Deterioro cognitivo leve (alt.funcional)
  - Demencia (alt estructural)

EVOLUCIÓN DIAGNÓSTICA

1984

NINCDS ADRDA

- Entidad **clinicopatológica**
- Dx probabilístico
- Fase de demencia

2007
2014

IWG 1 y 2

- Entidad **clinicobiológica**
- Dx: síndrome compatible + biomarcadores Alzheimer
- Dx in vivo
- Introducción **biomarcadores**
- Fase **prodrómica** / demencia

2011

NIA-AA

- Práctica clínica
- Niveles probabilísticos según biomarcadores
- "AD preclínica"

2018

NIA-AA AT(N)

- Entidad **biológica**
- Definida por biomarcadores

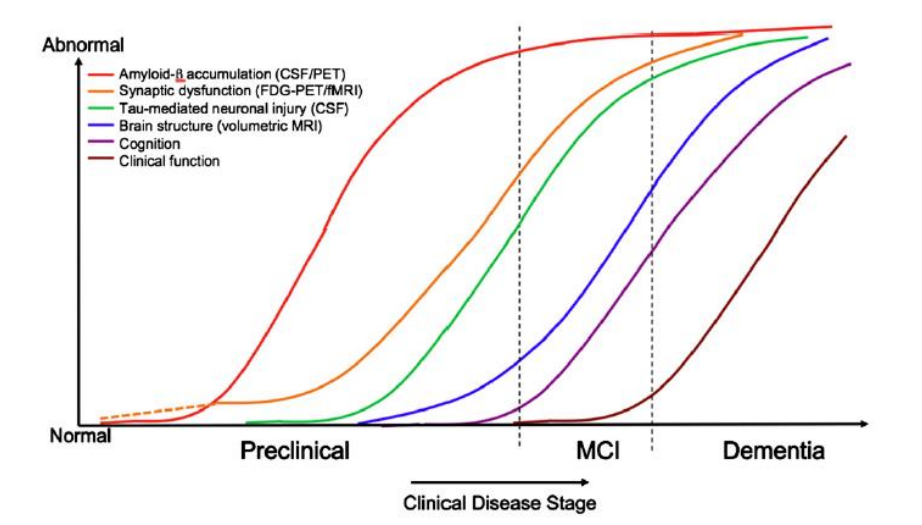
BIOMARCADORES

AT(N) category	CSF	Imaging
A: aggregated Aβ or associated pathologic state	↓$A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio	Amyloid-PET
T: aggregated tau (neurofibrillary tangles) or associated pathologic state	↑p-tau	Tau-PET
(N): neurodegeneration or neuronal injury	↑t-tau	Anatomic MRI FDG-PET

Jack CR. *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease.* Alzheimers Dement, 2018.

EVOLUCIÓN DIAGNÓSTICA

- Definición **biológica** (sistema ATN)
  - A: amiloide
  - T: tau
  - N: neurodegeneración
  - Otros: inflamación, vascular, sinucleína…



Biomarker profiles and categories

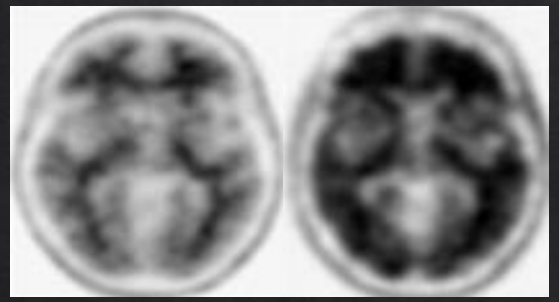
AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Jack CR. *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease.* Alzheimers Dement, 2018.

BIOMARCADORES de imagen

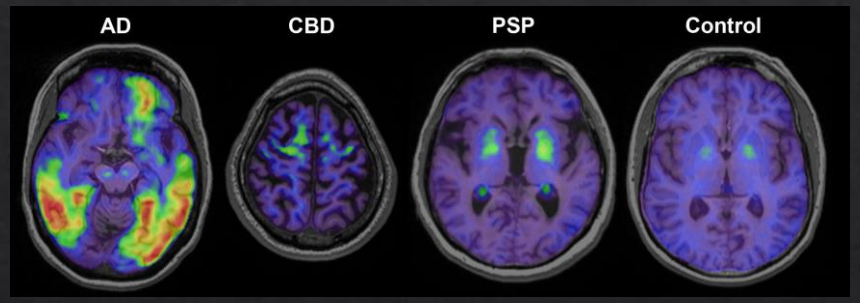
- **Imagen/medicina nuclear**

A: PET-amiloide



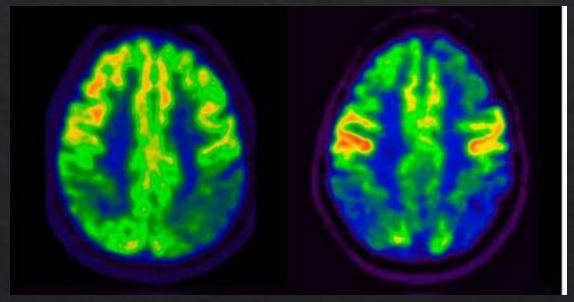
Lectura binaria
S: 96%, E: 100% placas neuríticas (>= moderada)

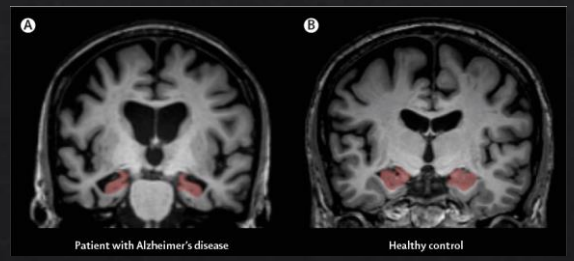
T: PET-tau



Escasa disponibilidad – investigación
Aprobado FDA (flortaucipir)
Utilidad pronóstica / estadiaje
Temporal medial → cortical
¿Otras taupatías?

N: PET-FDG, RM

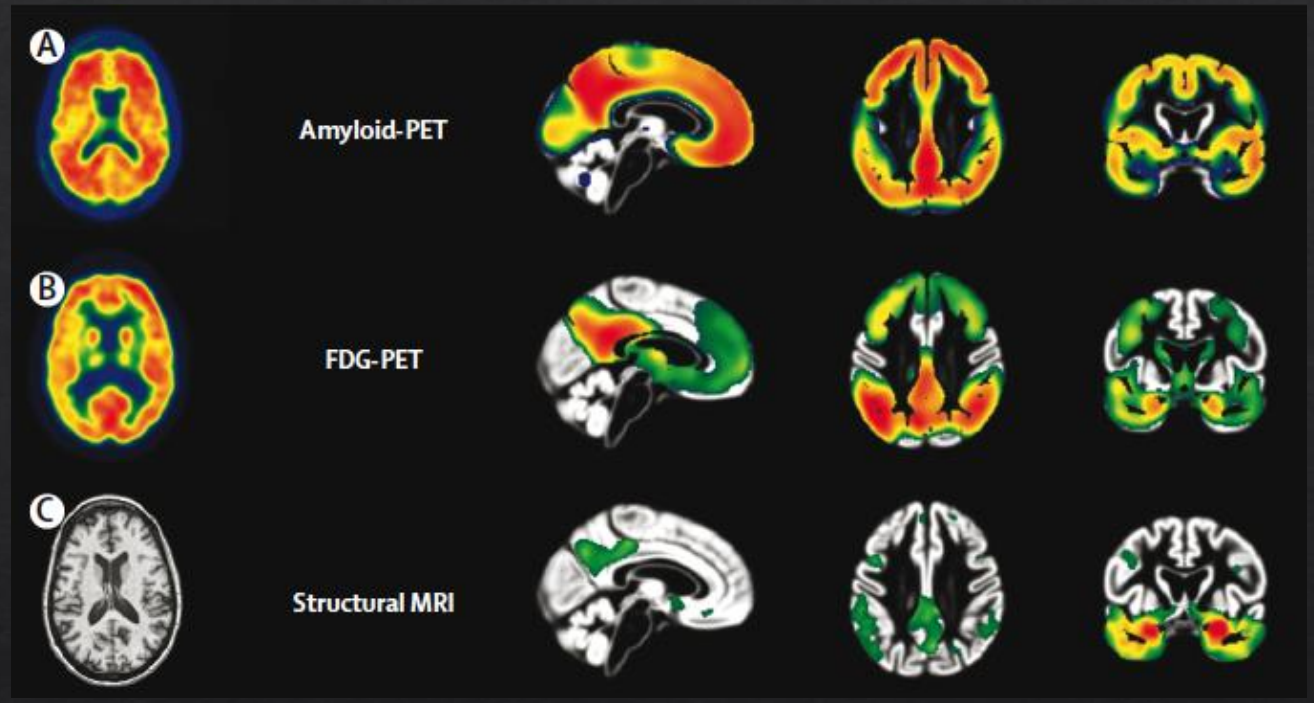




Multimodal imaging in Alzheimer's disease: validity and usefulness for early detection

Stefan Teipel, Alexander Drzezga, Michel J Grothe, Henryk Barthel, Gaël Chételat, Norbert Schuff, Pawel Skudlarski, Enrica Cavedo, Giovanni B Frisoni, Wolfgang Hoffmann, Jochen René Thyrian, Chris Fox, Satoshi Minoshima, Osama Sabri, Andreas Fellgiebel

Lancet Neurology Oct 2015

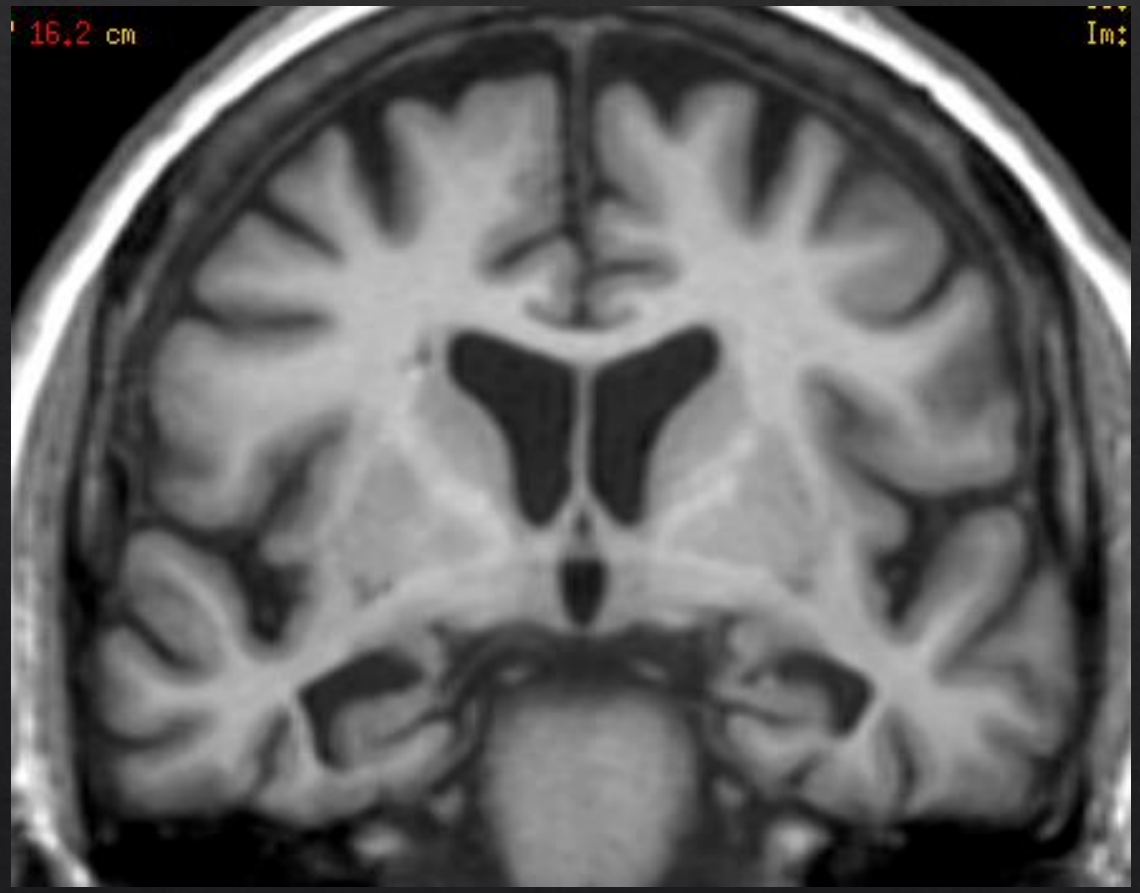


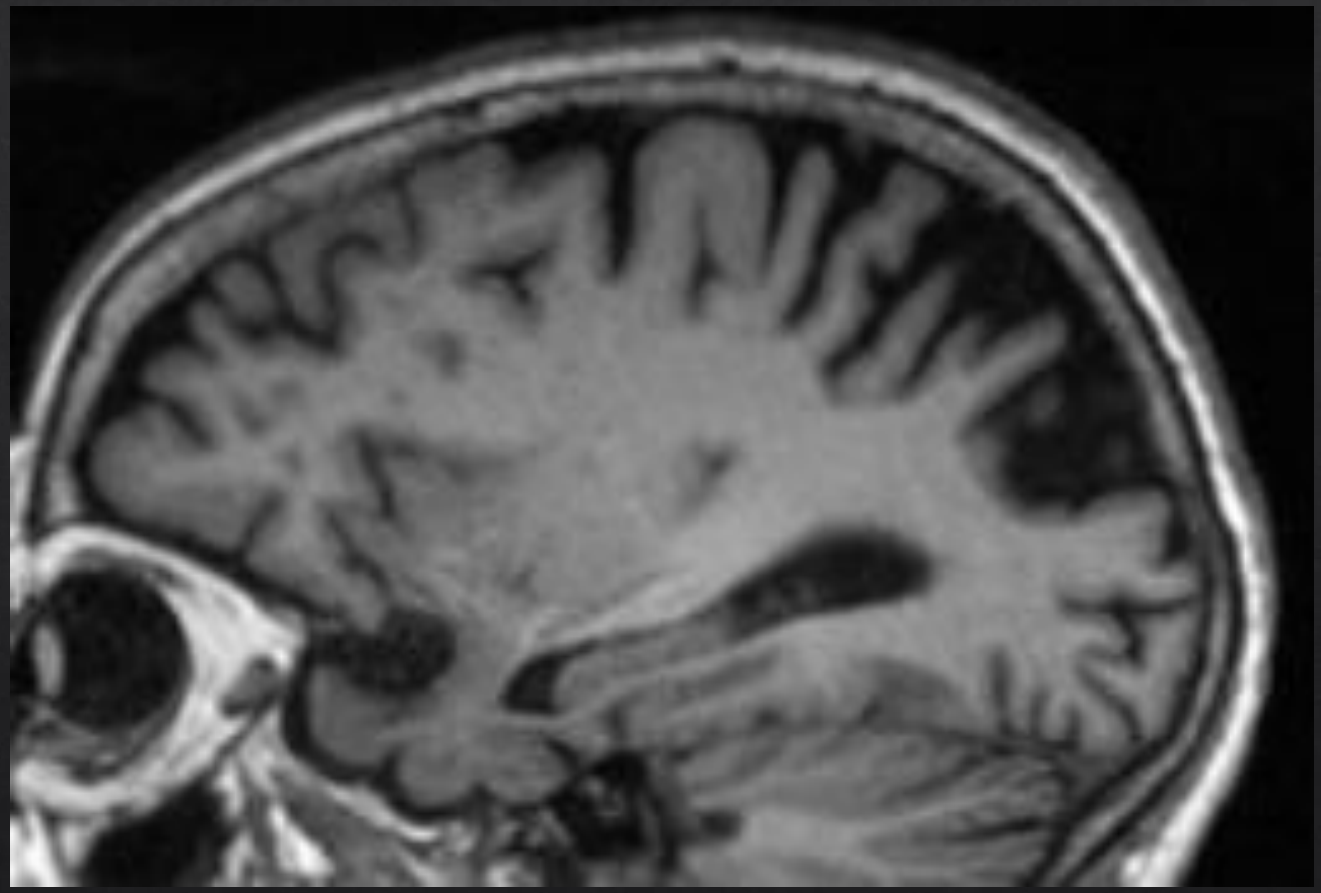
Amiloide> sensible
FDG> específico
RMe > conversión

No hay indicaciones clínicas definidas de uso combinado

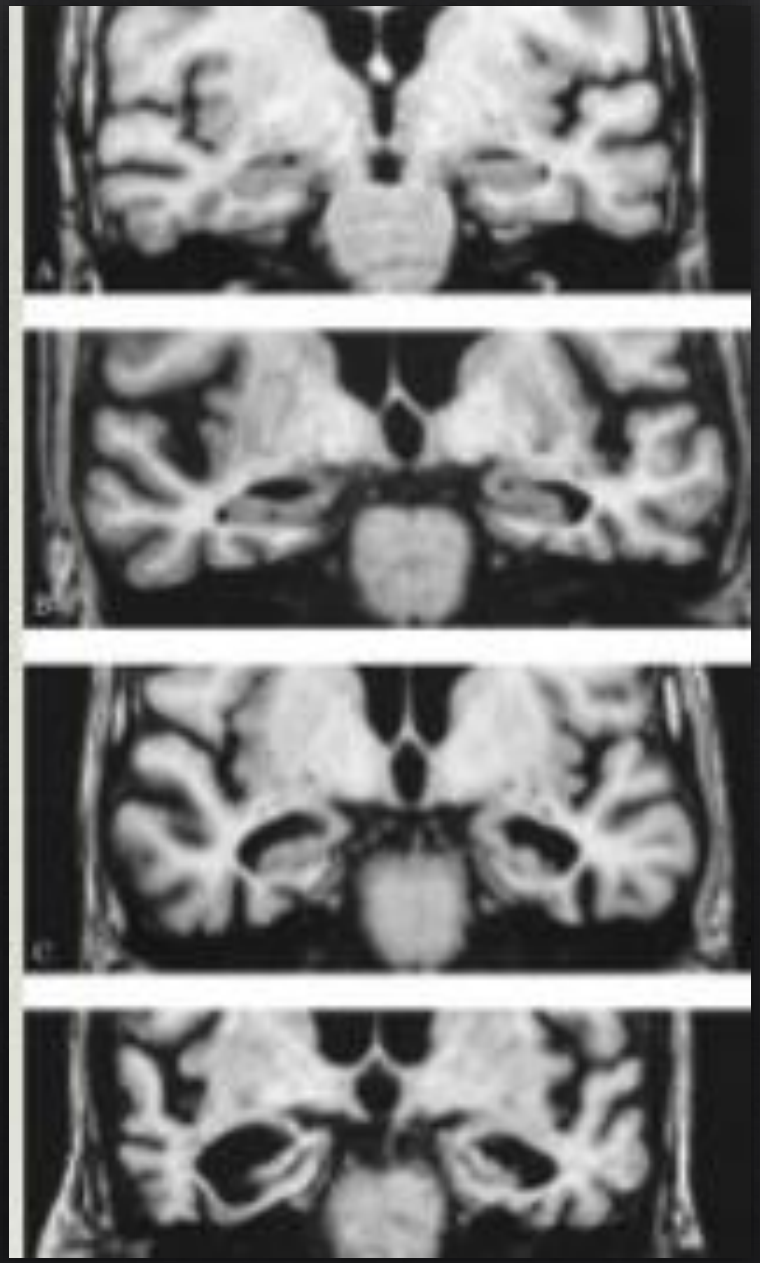
In our view, combinations of neuroimaging biomarkers (MRI and PET or FDG and amyloid PET) are more accurate in predicting conversion from mild cognitive impairment to Alzheimer's disease than any marker alone, suggesting that they provide complementary rather than redundant information.

Atrofia de predominio temporal medial/parietal





Grados de Scheltens

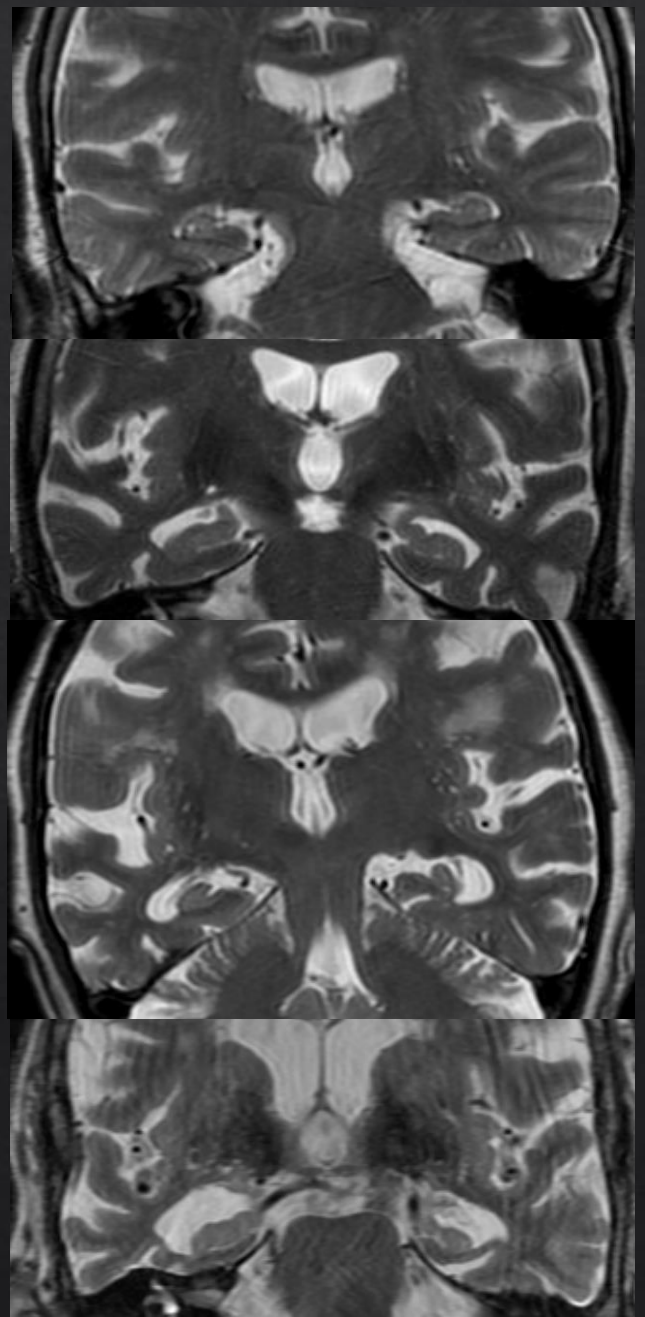


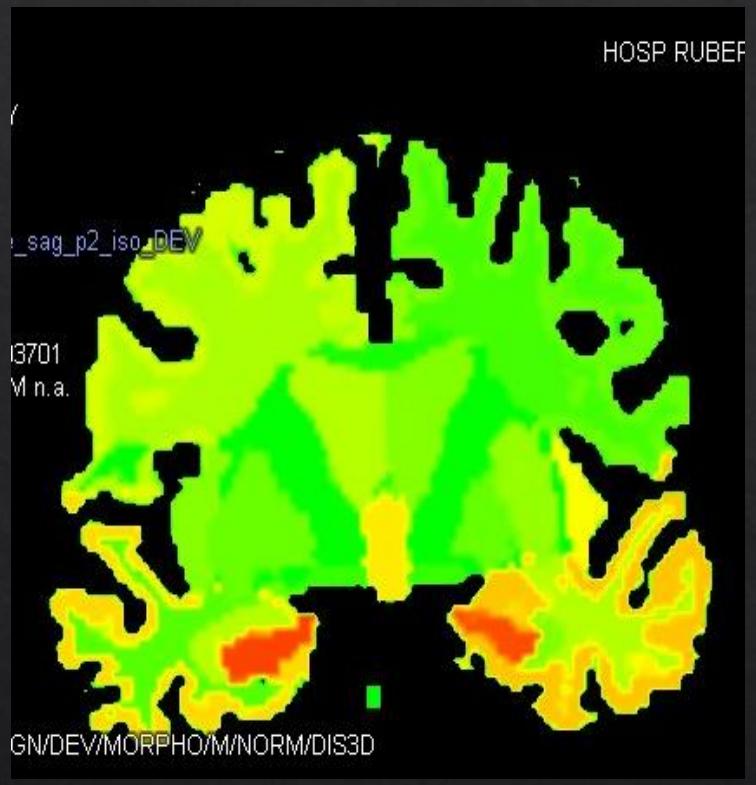
Grado 1:
- ↑C. Coroidea

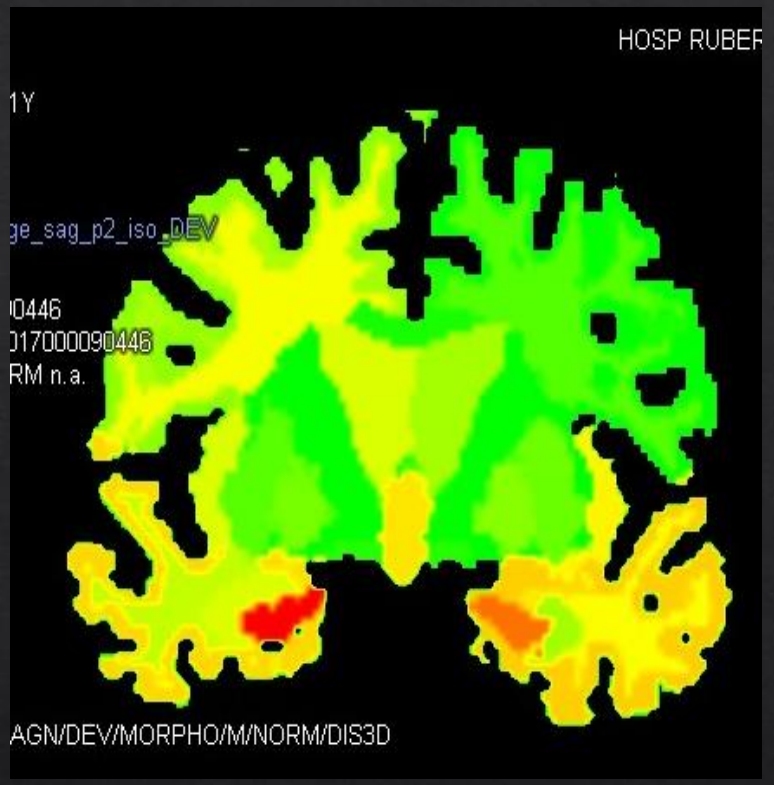
Grado 2:
- ↑C.Coroidea
- ↑Asta Temporal

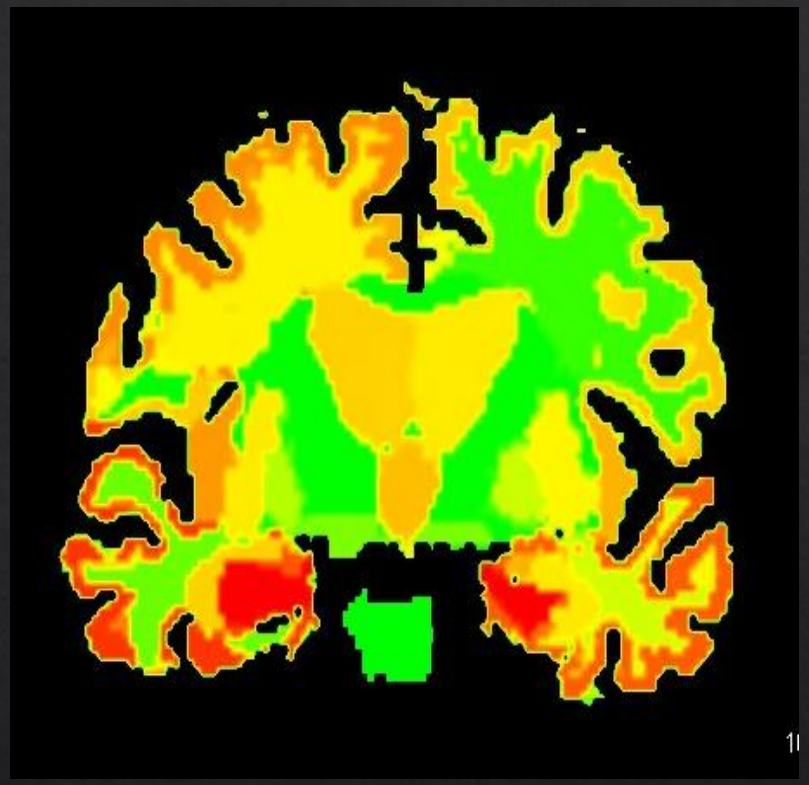
Grado 3:
- ↑C. Coroidea
- ↑Asta Temporal
- ↓Hipocampo

Grado 4:
- ↑C. Coroidea
- ↑Asta Temporal
- ↓↓Hipocampo



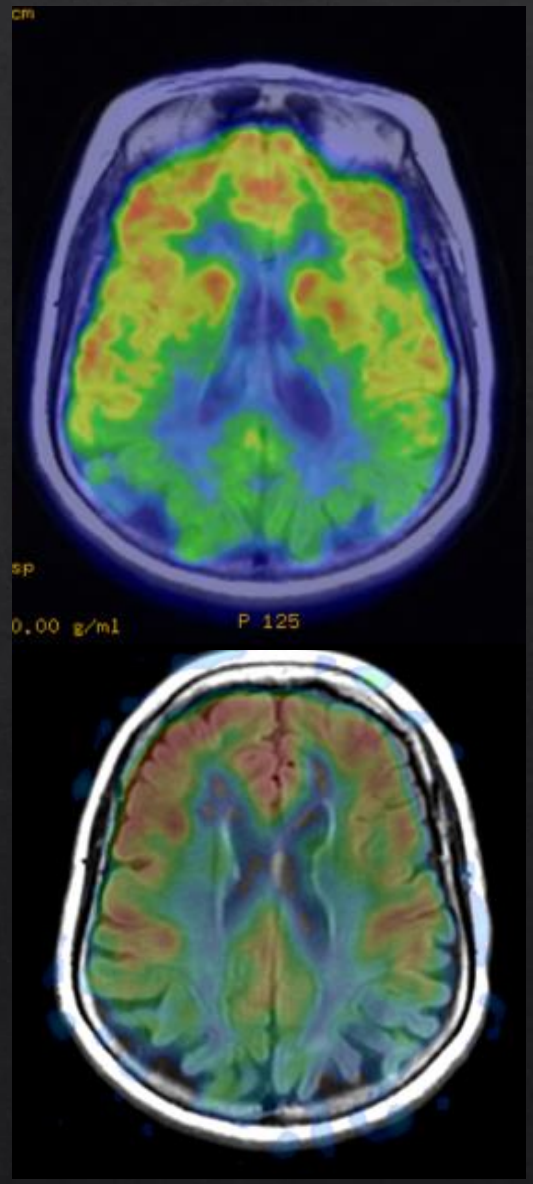

HOSP RUBEF
_sag_p2_iso_DEV
3701
M n.a.
GN/DEV/MORPHO/M/NORM/DIS3D


HOSP RUBEF
1Y
ge_sag_p2_iso_DEV
0446
017000090446
RM n.a.
AGN/DEV/MORPHO/M/NORM/DIS3D

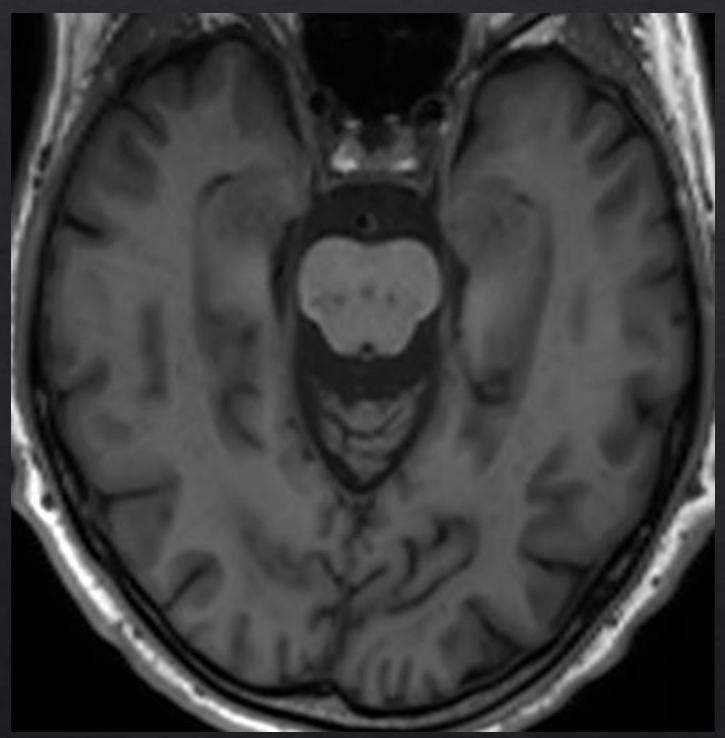


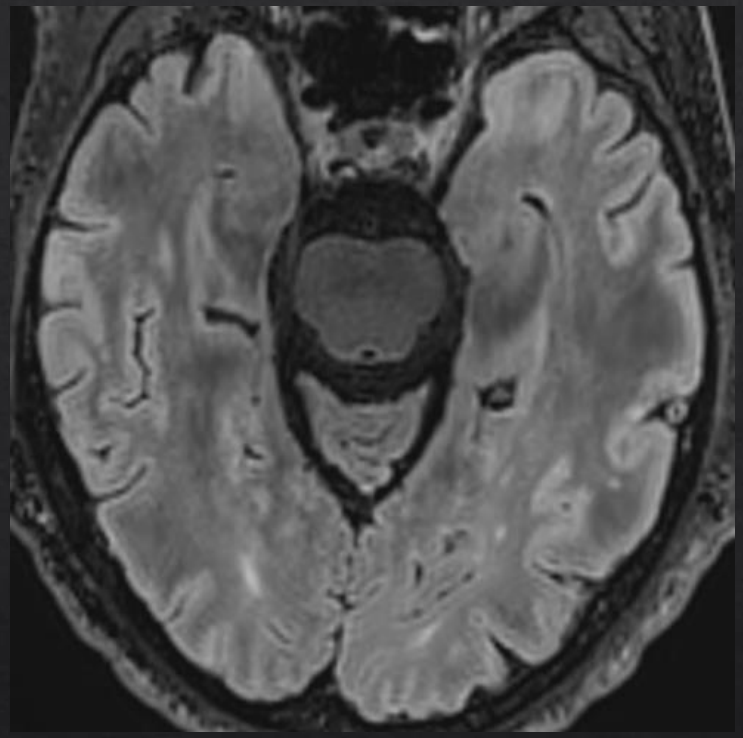
ASL en demencia

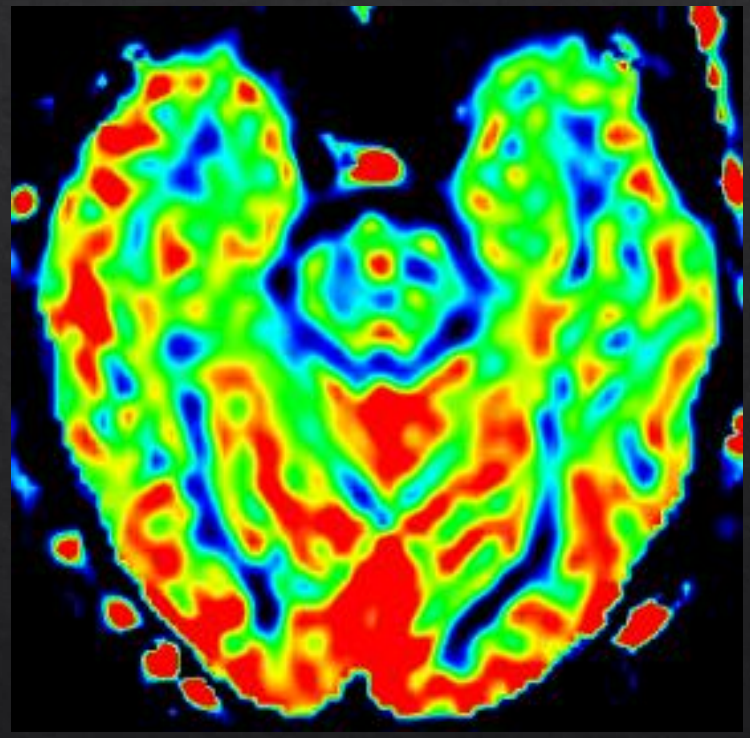
- Manejar Tiempo de inversión (BT y PLD)
- Controlar movimiento ; estudio rápido
- Alternativa a PET-FDG aunque menos sensible
- Utilidad
  - DCL: complemento a RM estructural
    - Reservar PET para ver Amiloide
  - Demencia: DDx
    - FTD: valorar amiloide con PET
    - DLB: Nigrosoma/DATscan



DCL

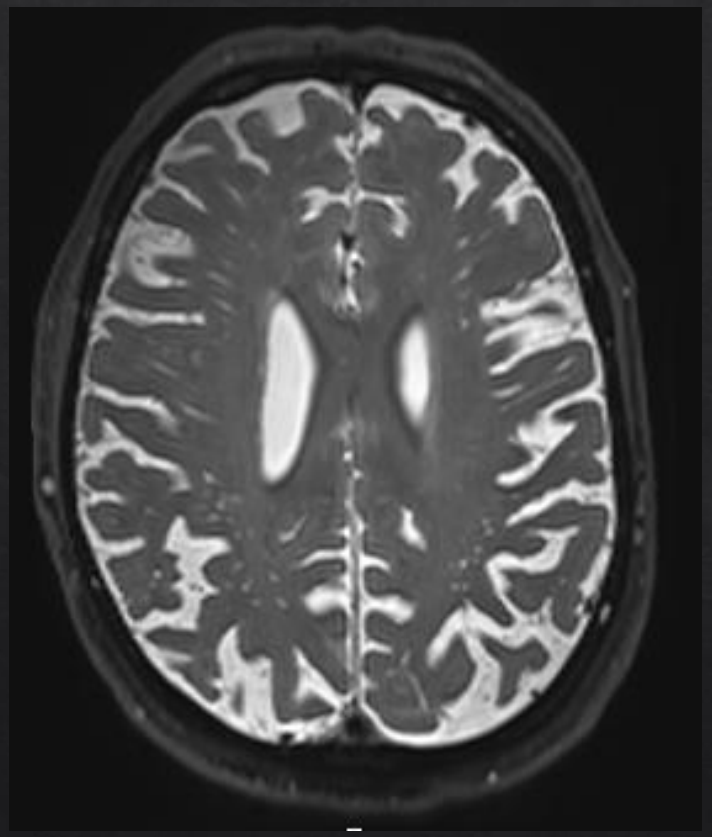


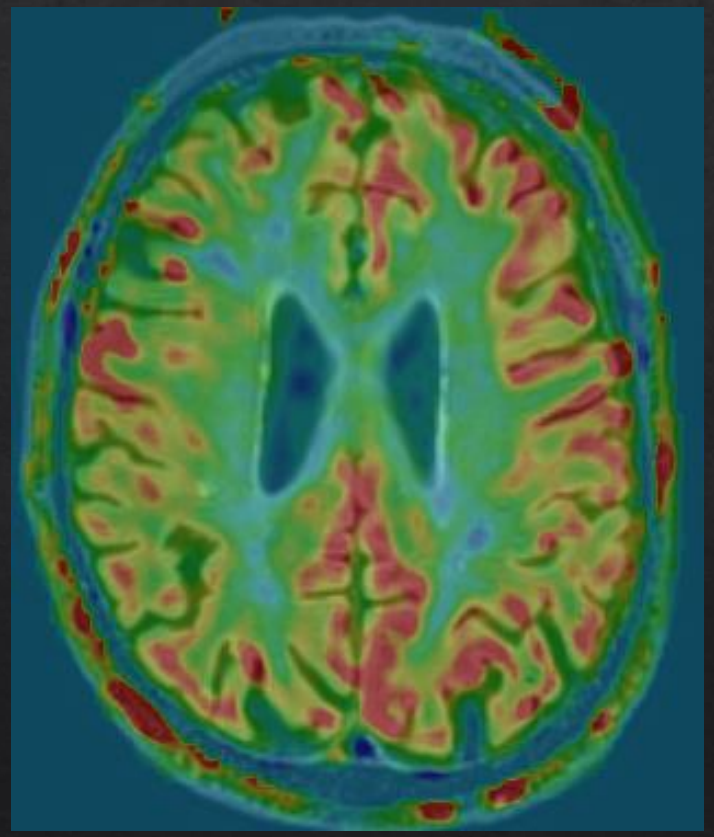


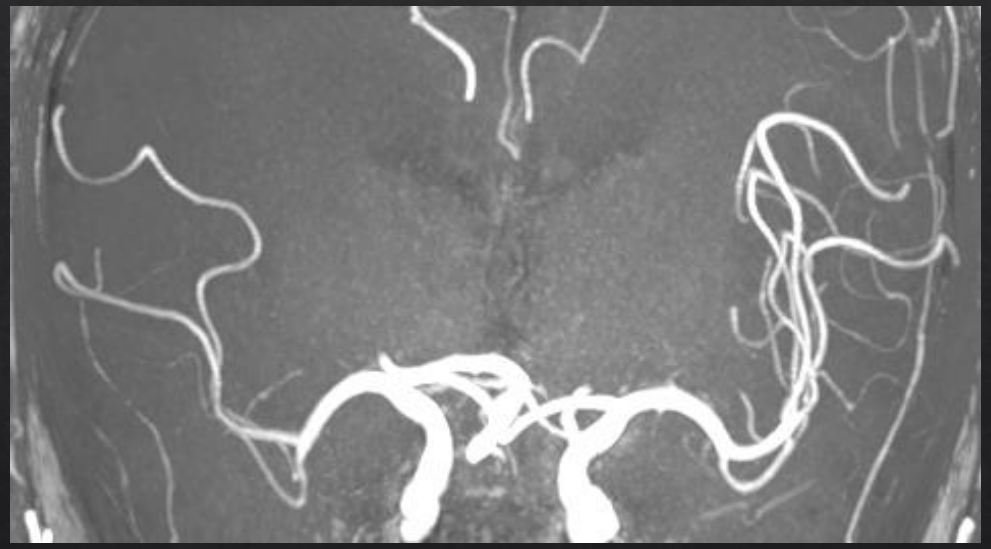


Un hallazgo en ASL no característico/congruente debe confirmarse con más exploraciones y/o excluir artefactos

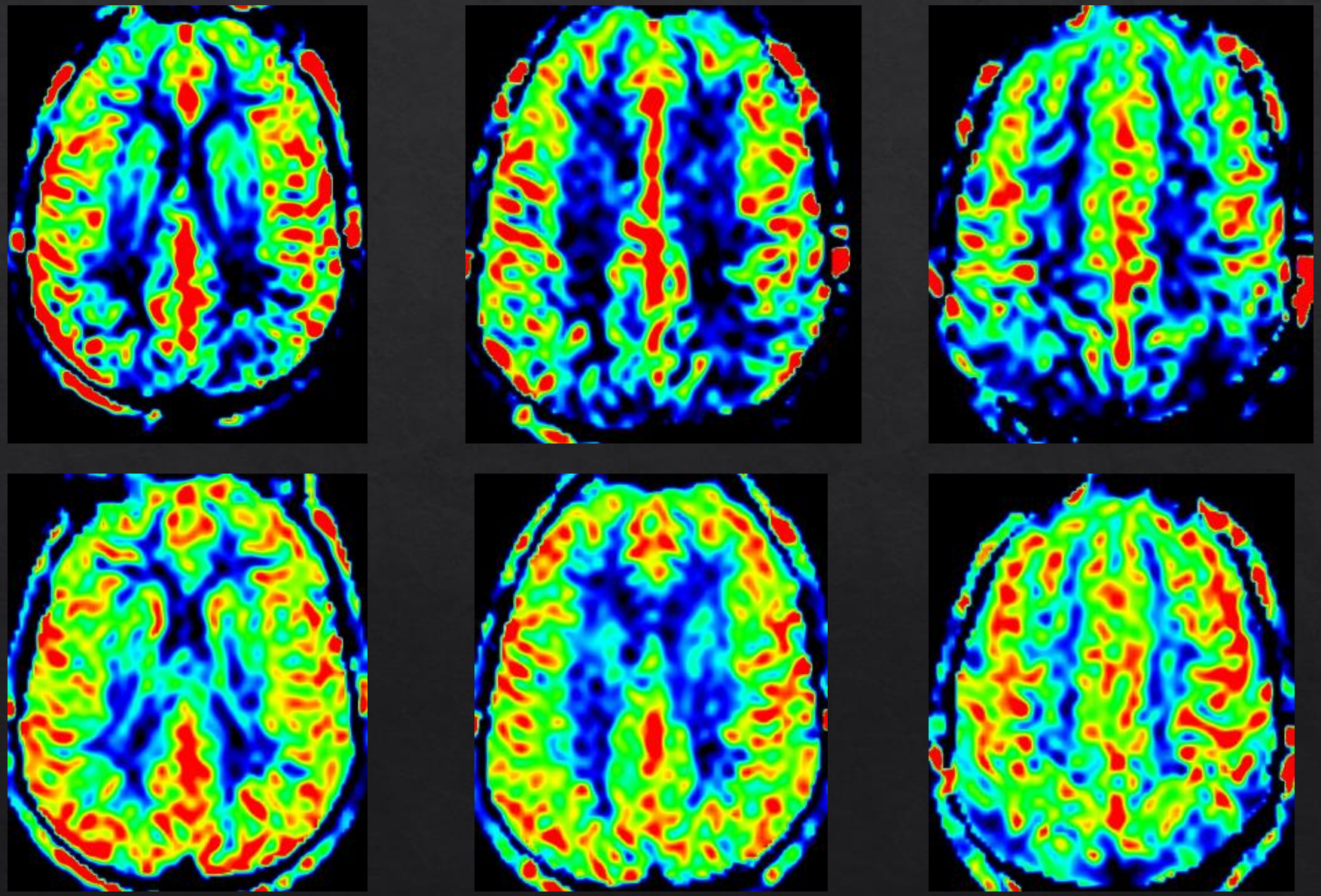
Demencia FT?



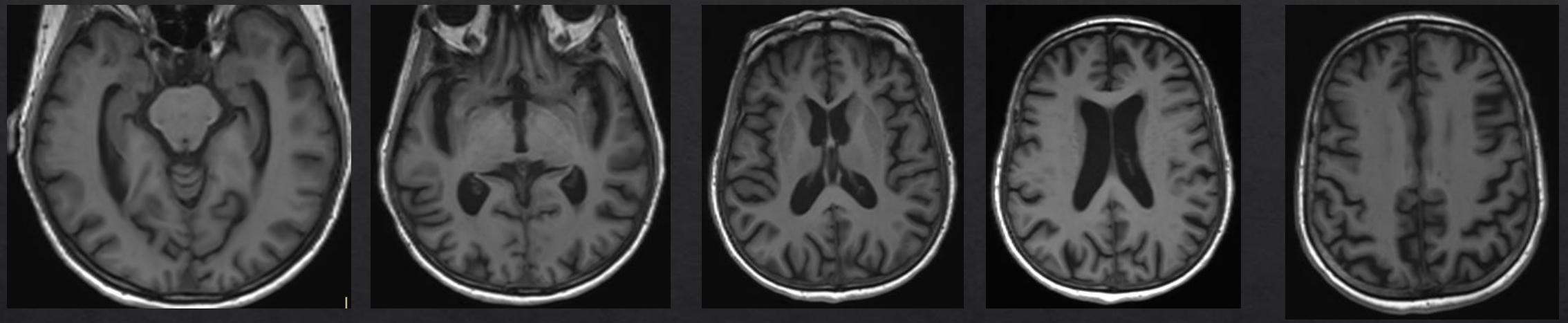


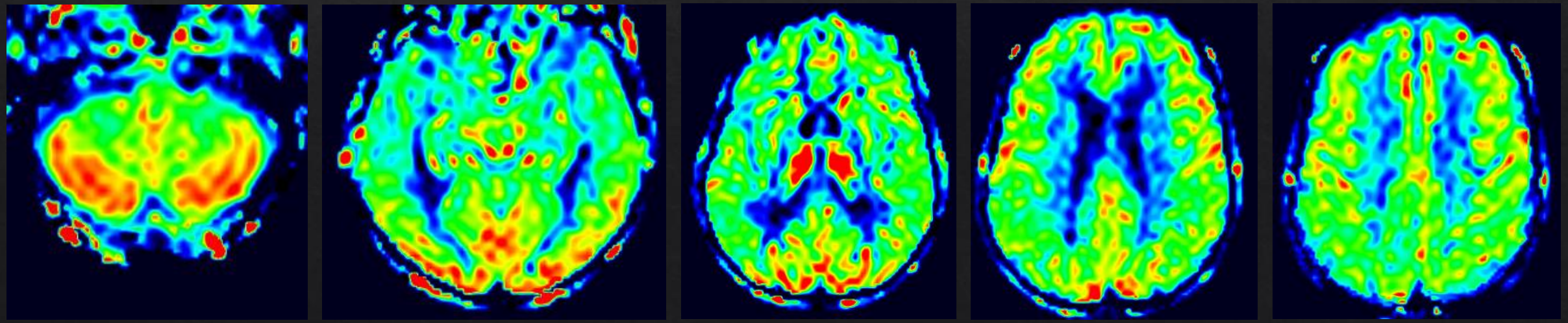


Ajuste de Tiempo de inversión

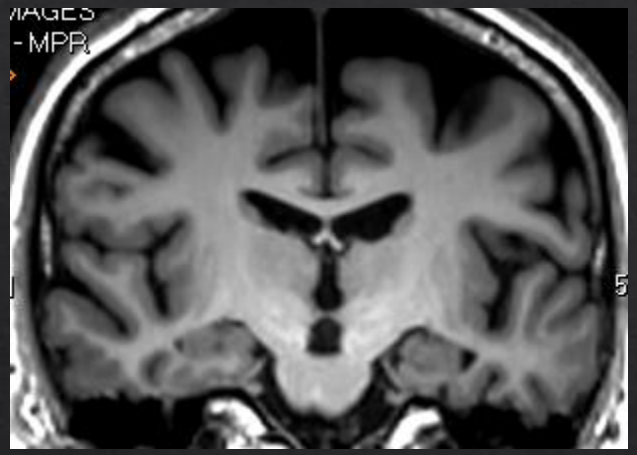


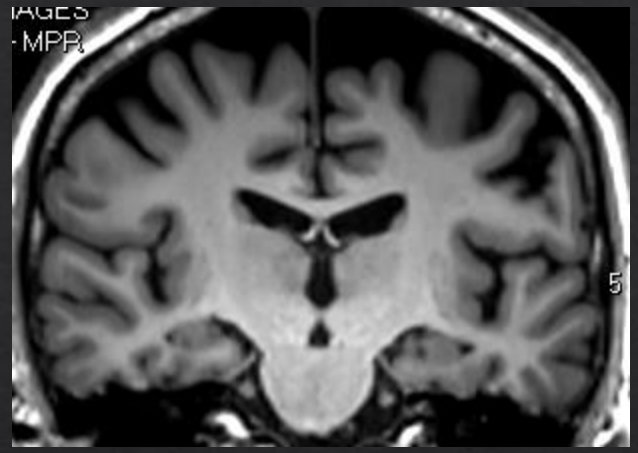
Hipoperfusion difusa

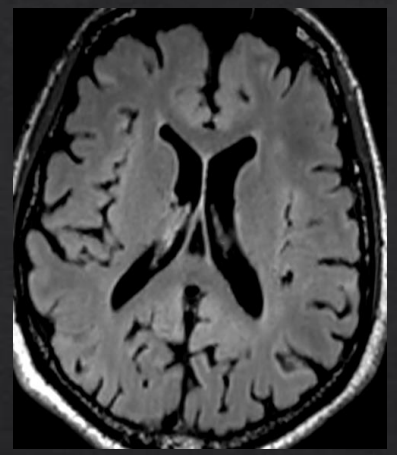


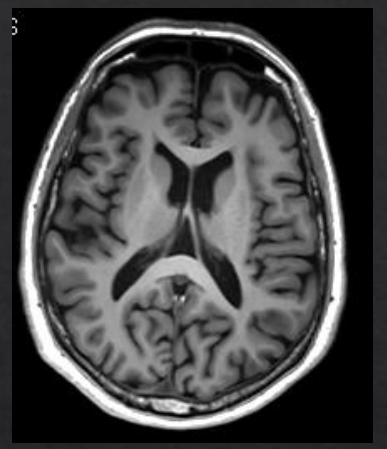


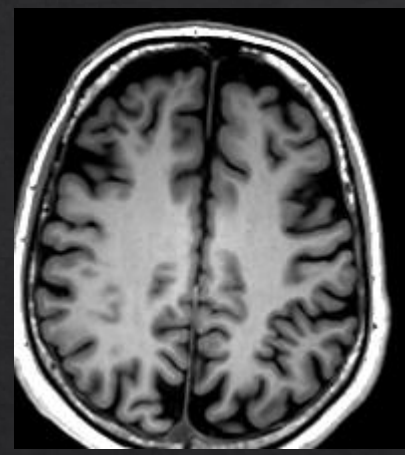
72 años, DCL, no atrofia

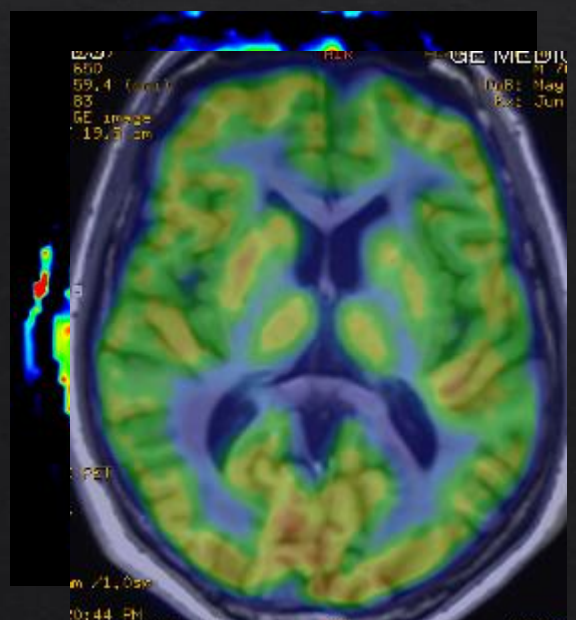


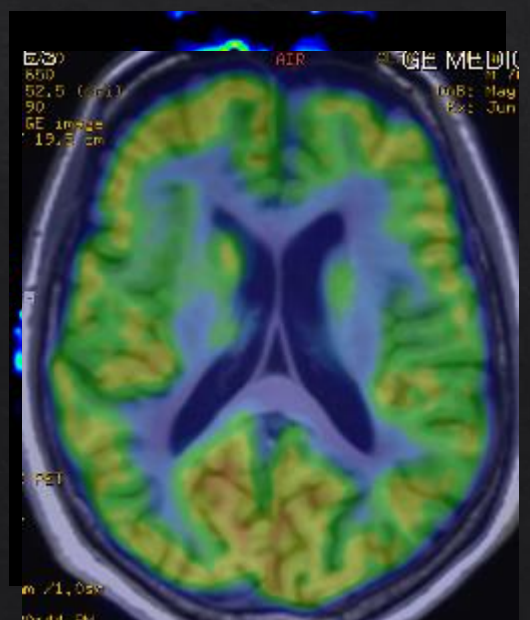


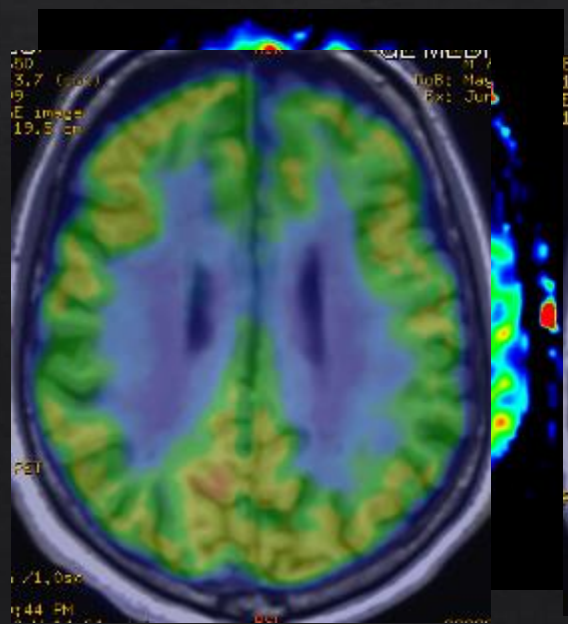


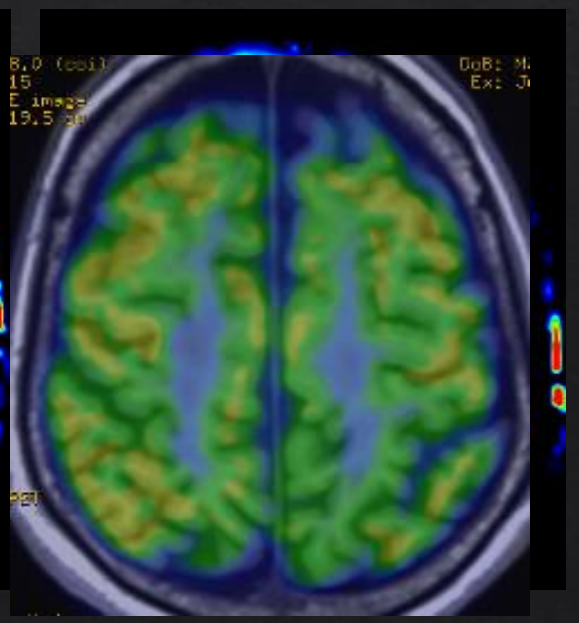




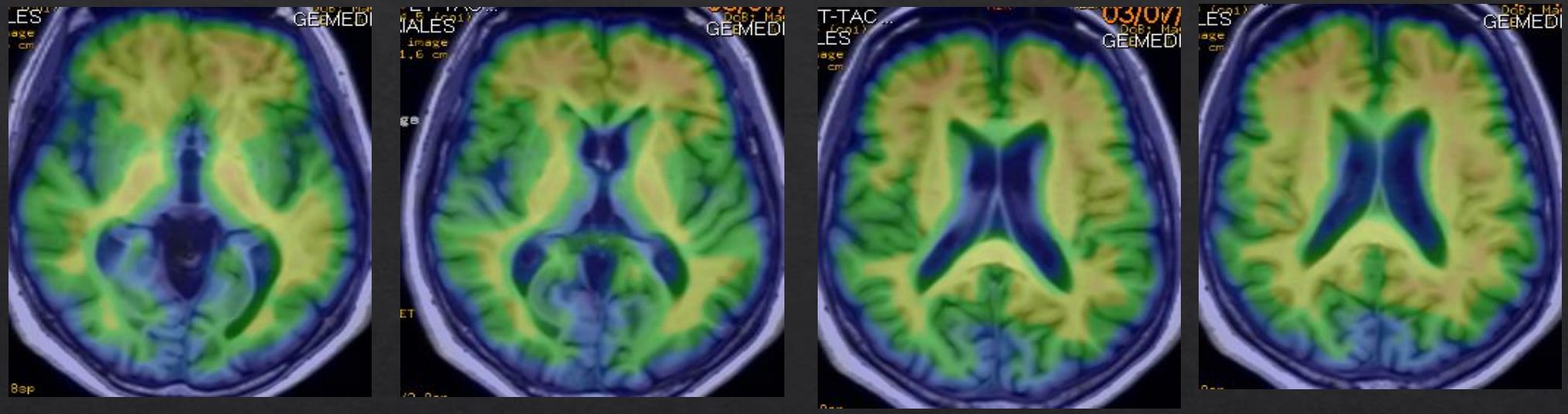








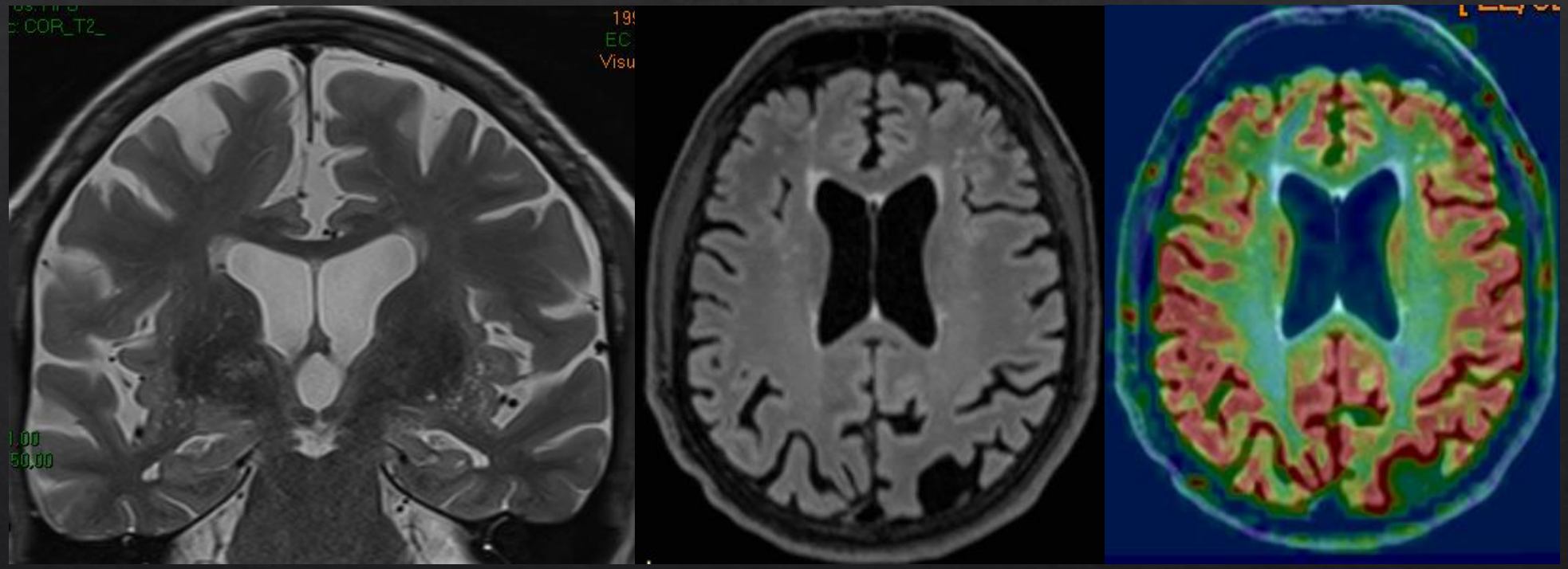
72 años, DCL, no atrofia



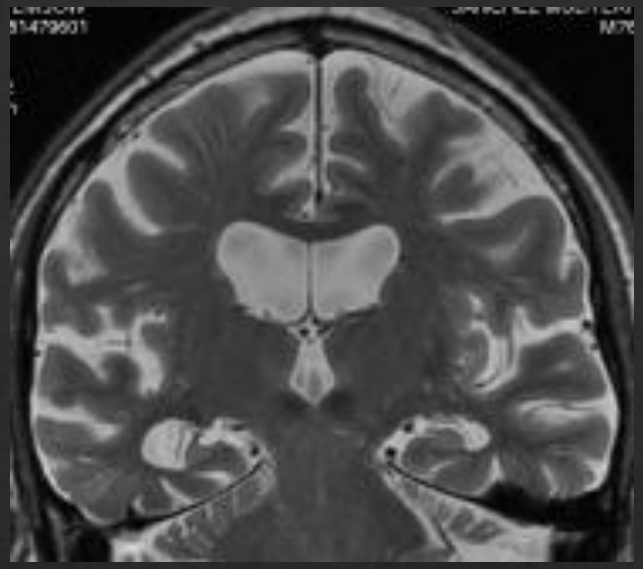
Utilidad del estudio funcional

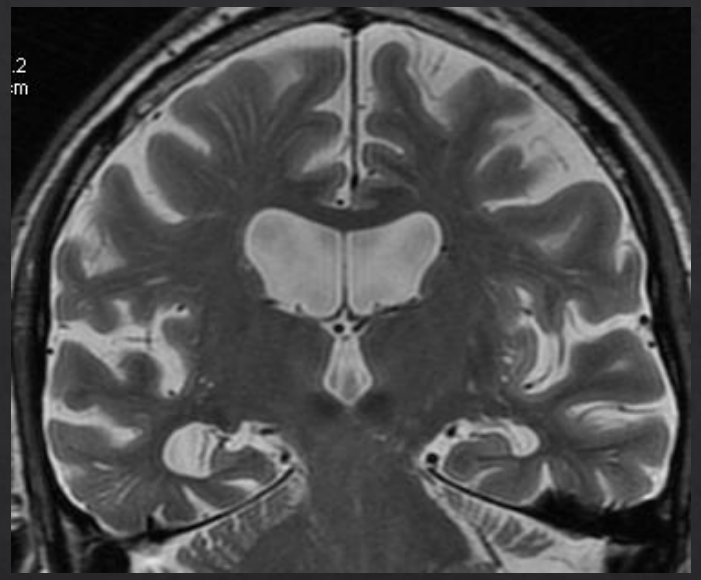
81 años
Quejas de memoria

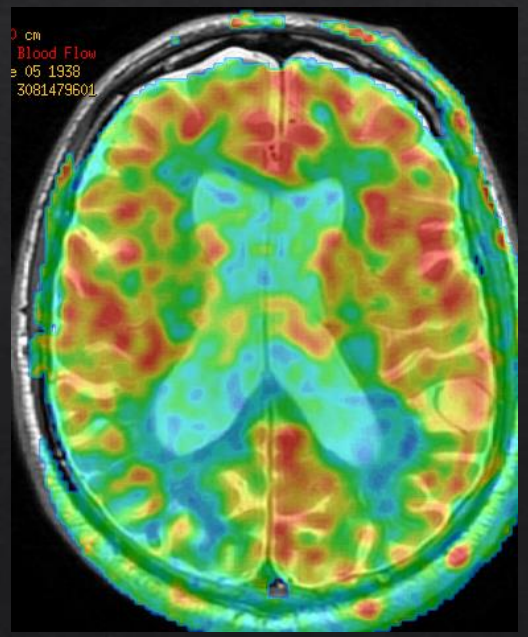
Discreta atrofia difusa

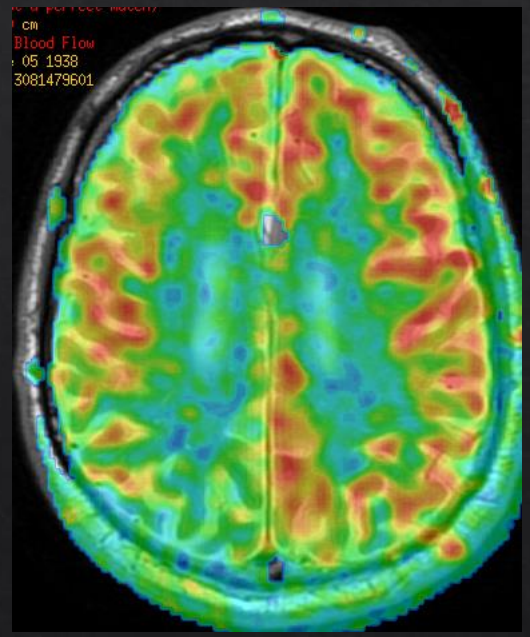


Un estudio funcional normal es muy poco probable en una enfermedad neurodegenerativa



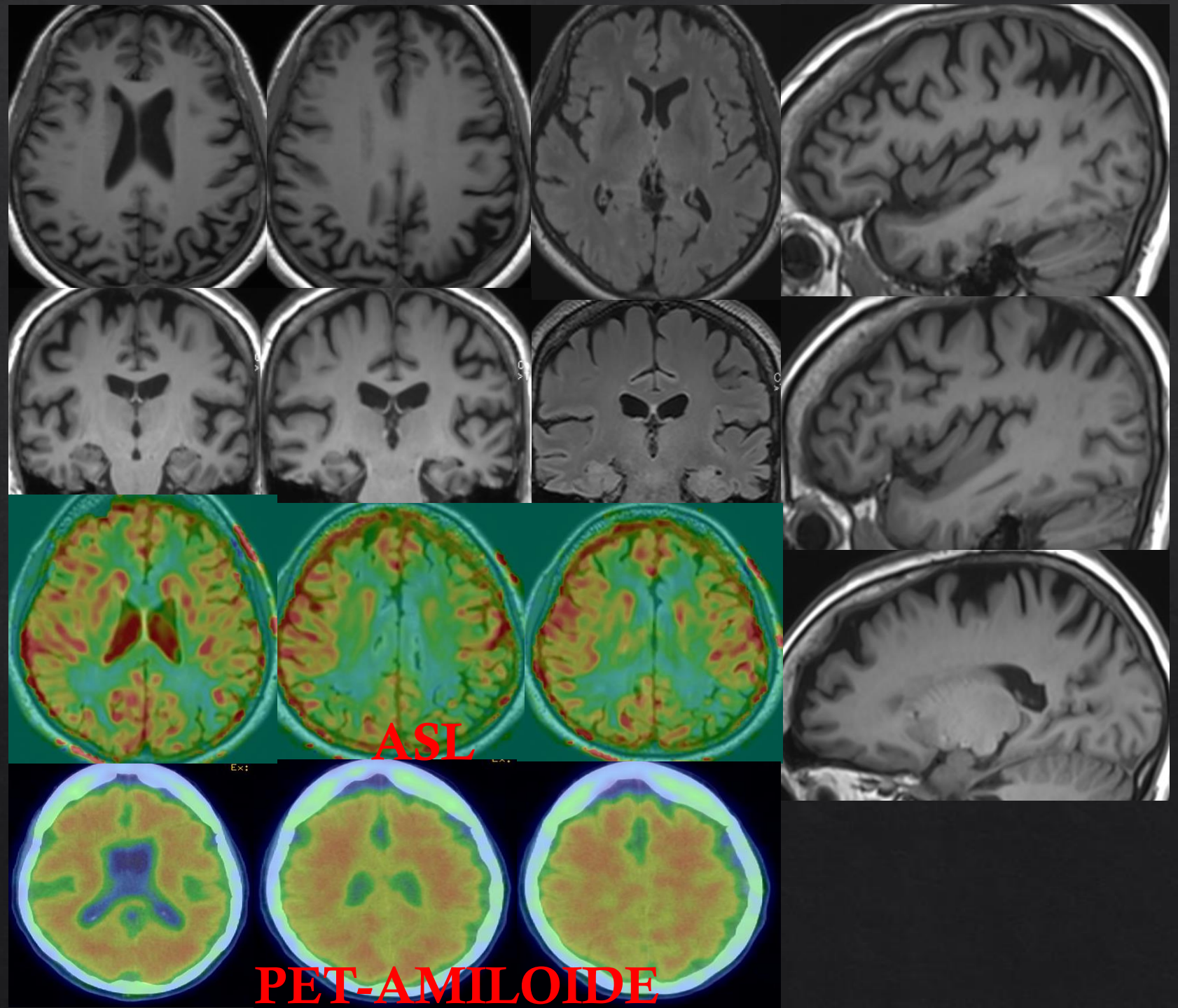






Un patrón funcional patológico característico sugiere enfermedad neurodegenerativa

Mujer 62 años
Alteración de memoria reciente que dificulta la vida independiente
Cambios de conducta
Apatía



Demencia con cuerpos de Lewy

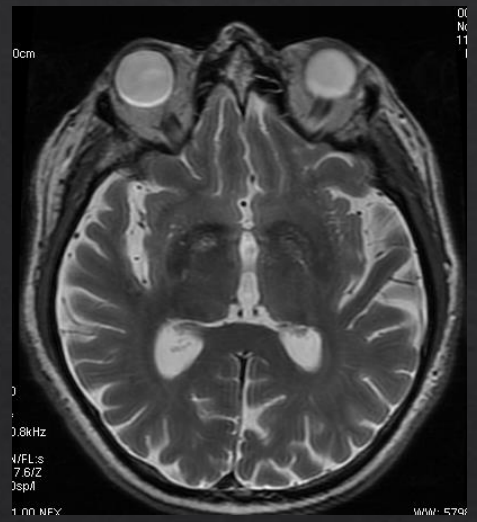
- Segunda causa de demencia degenerativa
  - 20% de todas las demencias (autopsia)
- Deterioro cognitivo fluctuante con alucinaciones visuales y Parkinson
- Predominio en hombres (2:1)
- Sinucleopatía
  - Lewy
  - Parkinson
  - MSA
- Inicialmente poca atrofia, no hay predominio temporal

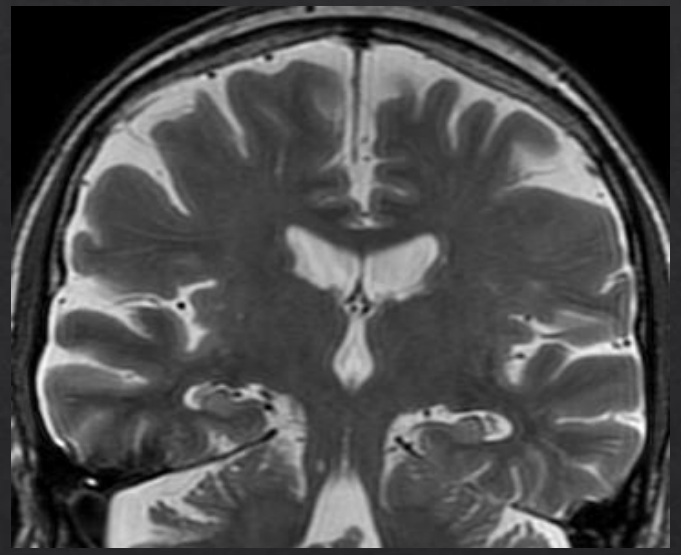
Criterios diagnósticos

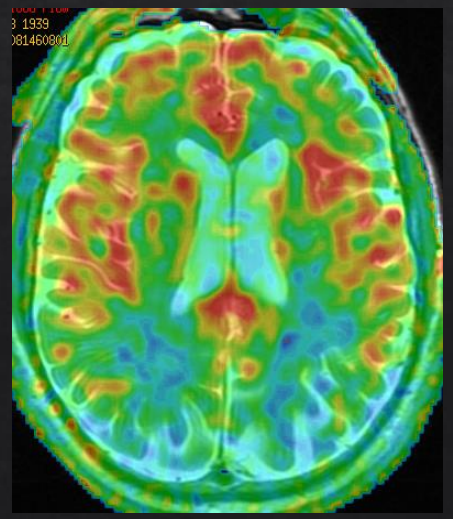
- Demencia, sin deterioro relevante inicial de memoria
- Rasgos primarios (2 probable, 1 posible)
  - Cognición fluctuante, especialmente de atención y alerta
  - Alucinaciones visuales recurrentes
  - Parkinsonismo espontáneo
- Criterios de apoyo
  - Hipersensibilidad a Neurolépticos
  - Trastornos conductuales en sueño REM
  - Caídas frecuentes
  - Síncopes
  - Ideas delirantes sistematizadas
  - Alucinaciones no visuales

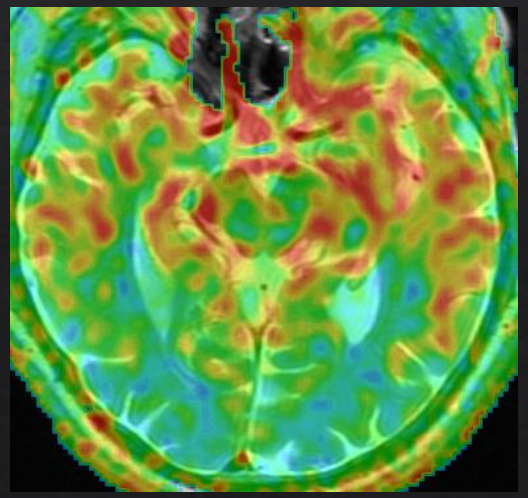
Imagen en Lewy

- RM: Hallazgos poco expresivos
  - Inicialmente no hay atrofia
  - En fases tardías atrofia difusa (no temporal)
- Imagen funcional
  - Hipofunción occipital
  - Frecuentemente Amiloide positivo
  - DAT-scan: ⬇Dopamina

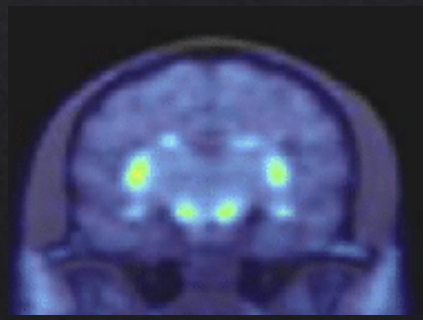


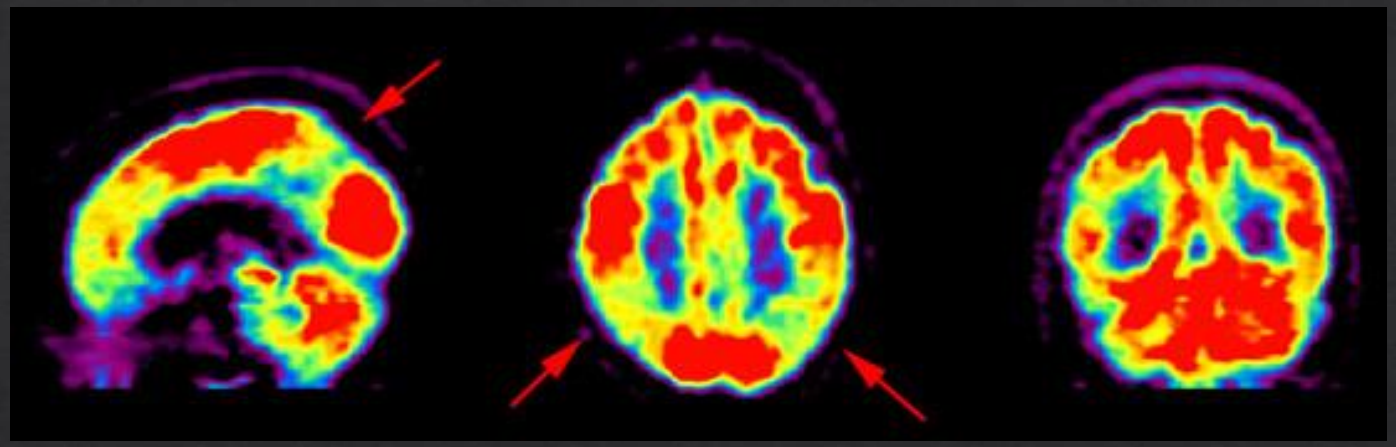




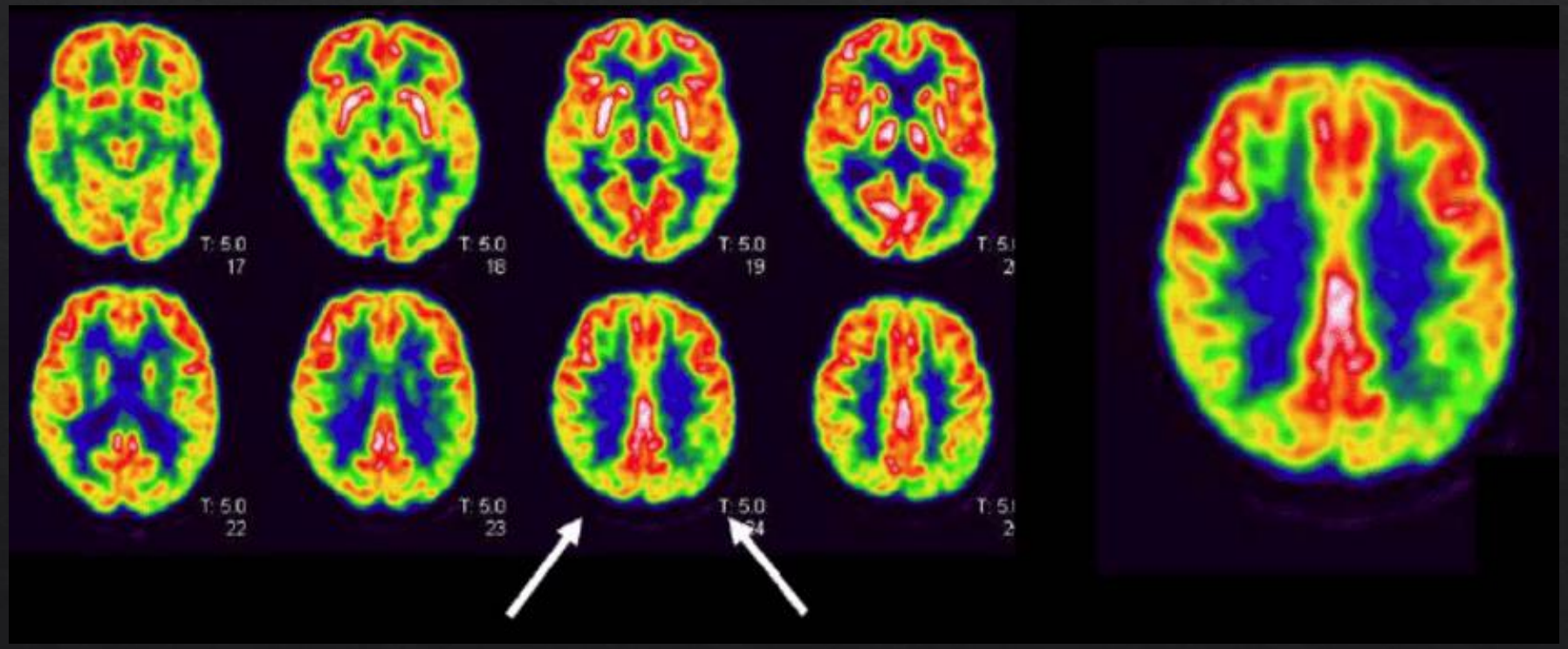


ASL





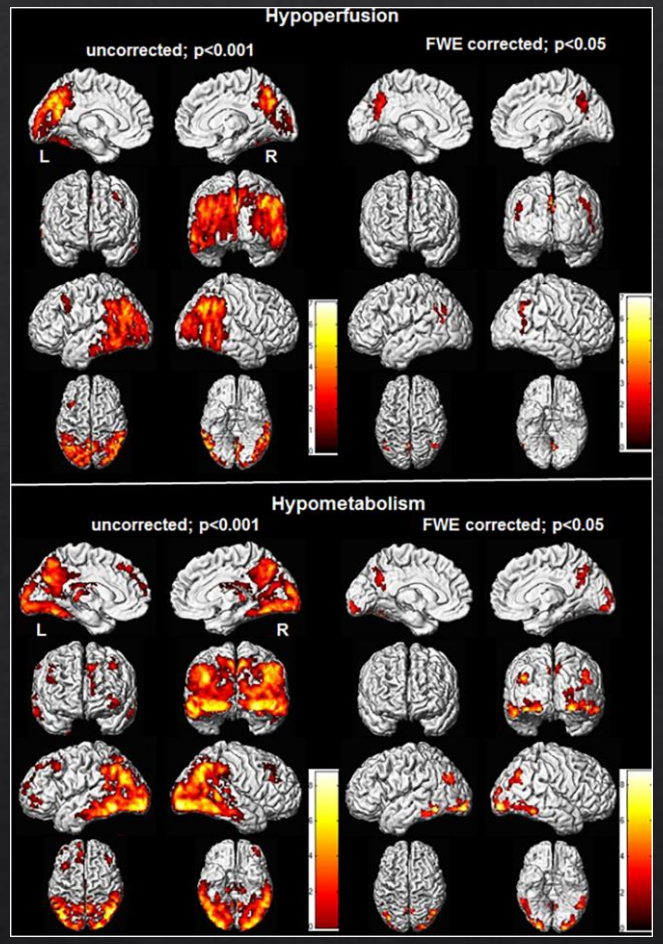
Alzheimer: hipometabolismo parietal y cingulo post

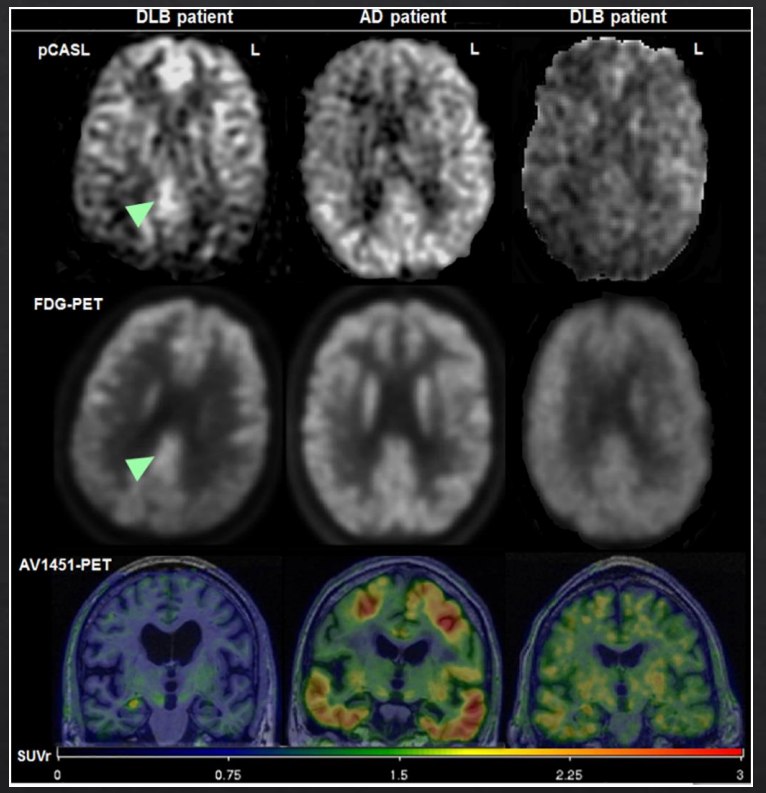


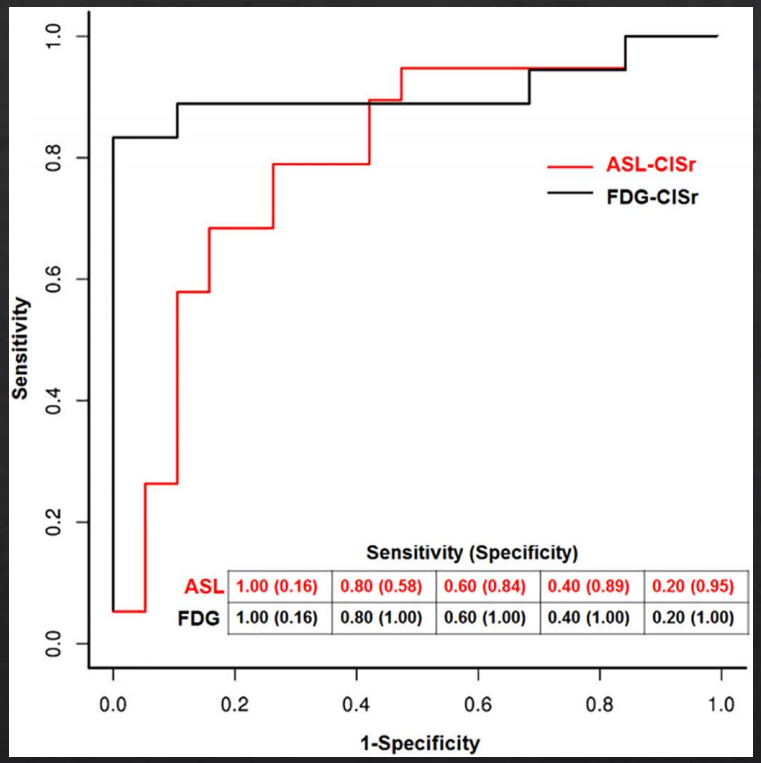
Lewy: hipometabolismo occipito-parietal. “Isla” en cíngulo posterior

Regional cortical perfusion on ASL in dementia with Lewy bodies: Associations with clinical severity, glucose metabolism and tau PET

Nedelska Neuroimage Clin 2018

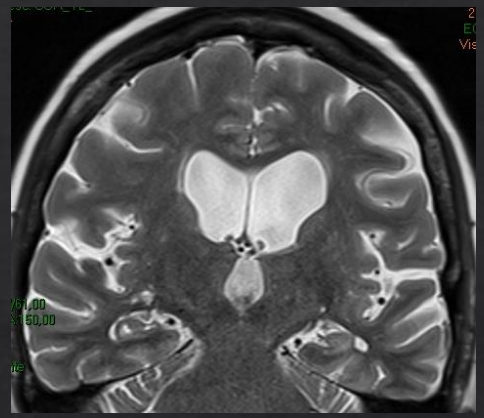


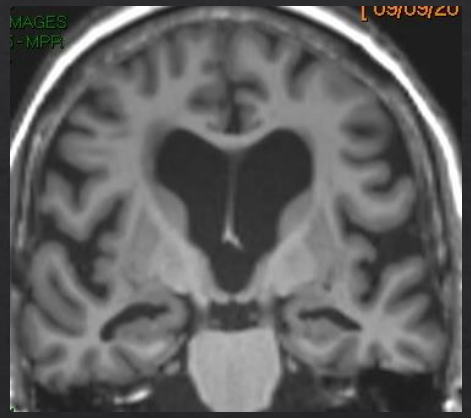


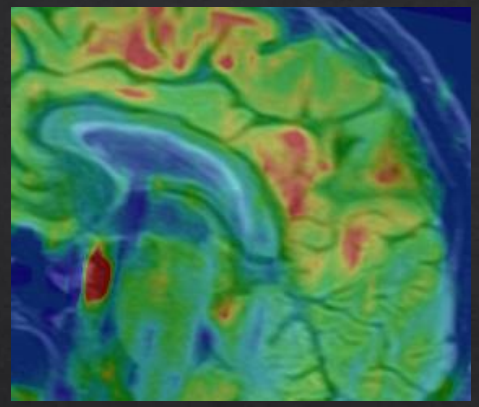


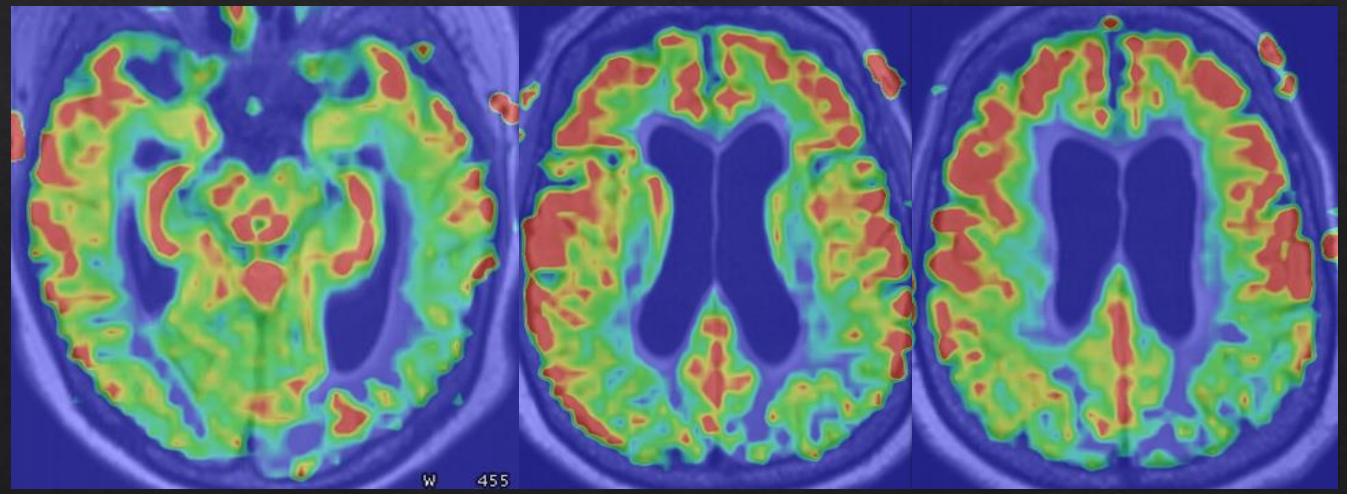
In summary, the pattern of cortical hypoperfusion on ASL-MRI is similar to hypometabolism on FDG-PET, and respective **cingulate island sign** ratios correlate with each other in DLB. Non-invasive and radiotracer-free ASL-MRI may be further developed as a tool for the screening and diagnostic evaluation of DLB patients in a variety of clinical settings where FDG-PET is not accessible.

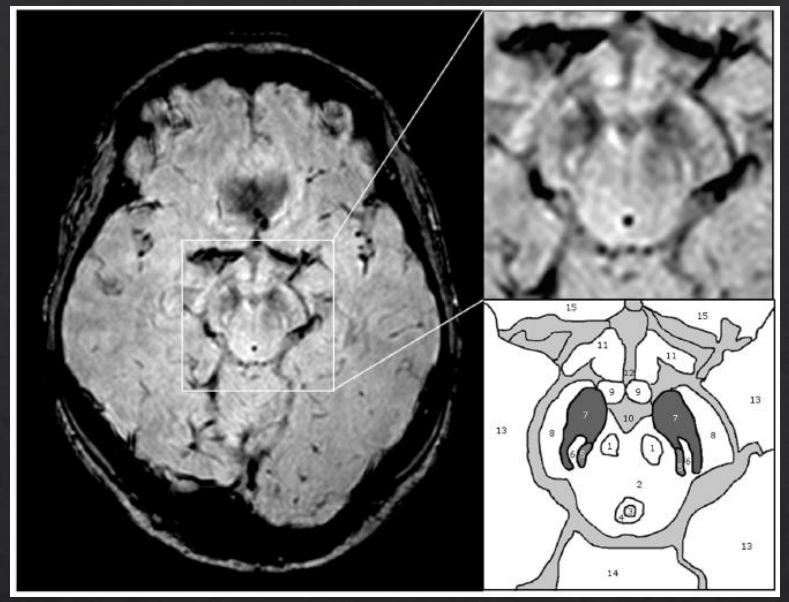
Demencia con Parkinson



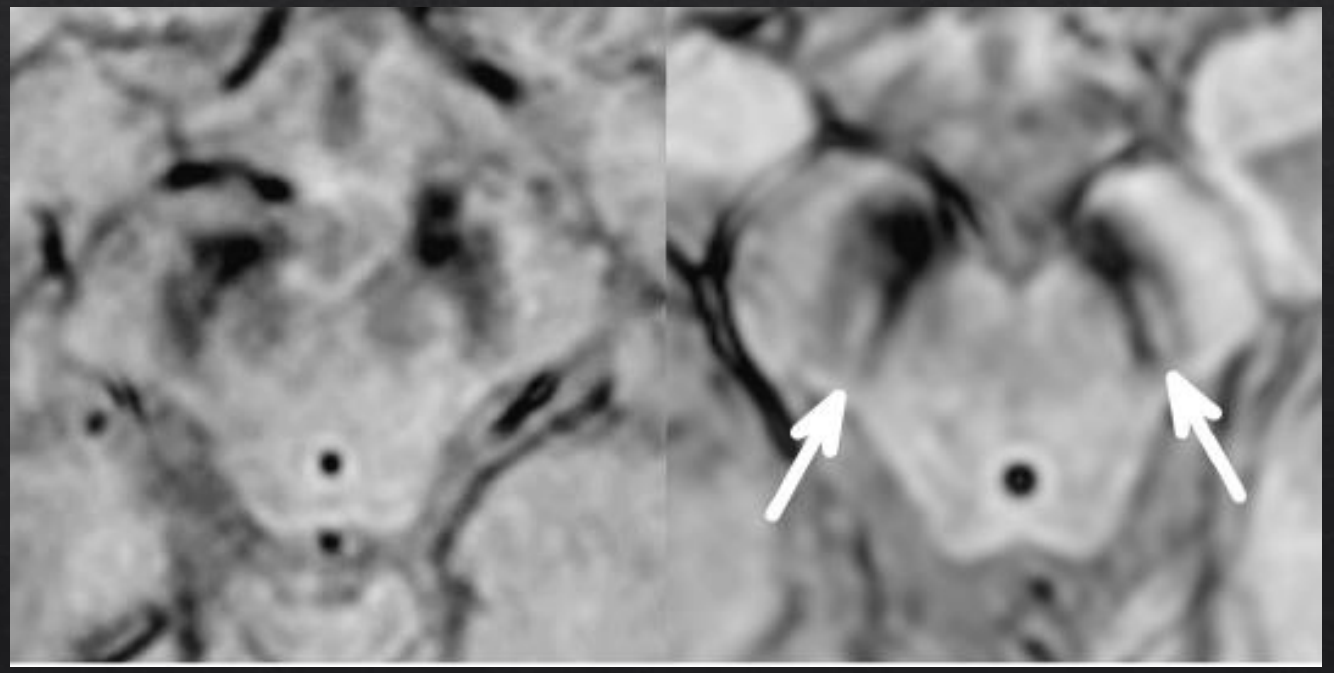


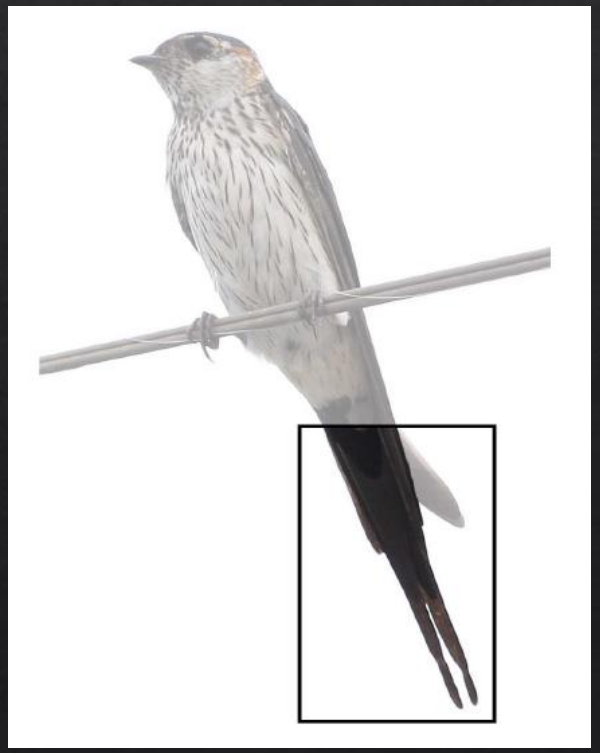




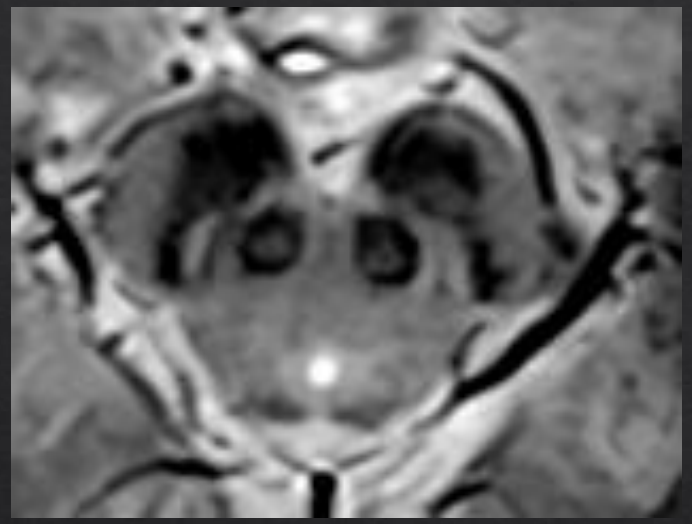


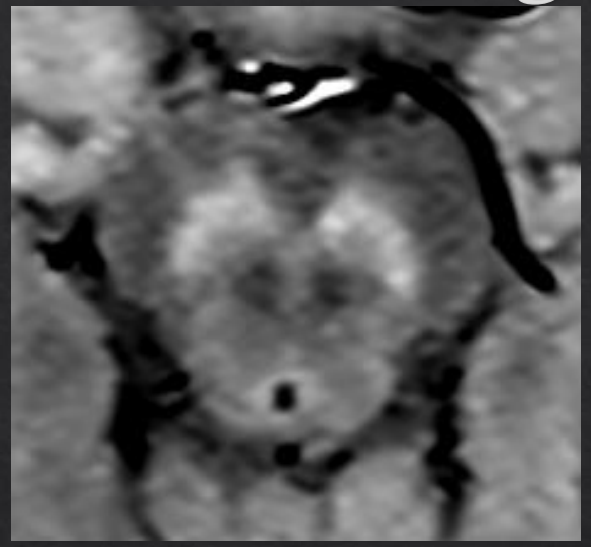
The ‘Swallow Tail’ Appearance of the Healthy Nigrosome – A New Accurate Test of Parkinson’s Disease: A Case-Control and Retrospective Cross-Sectional MRI Study at 3T
Schwarz PlosOne 2014

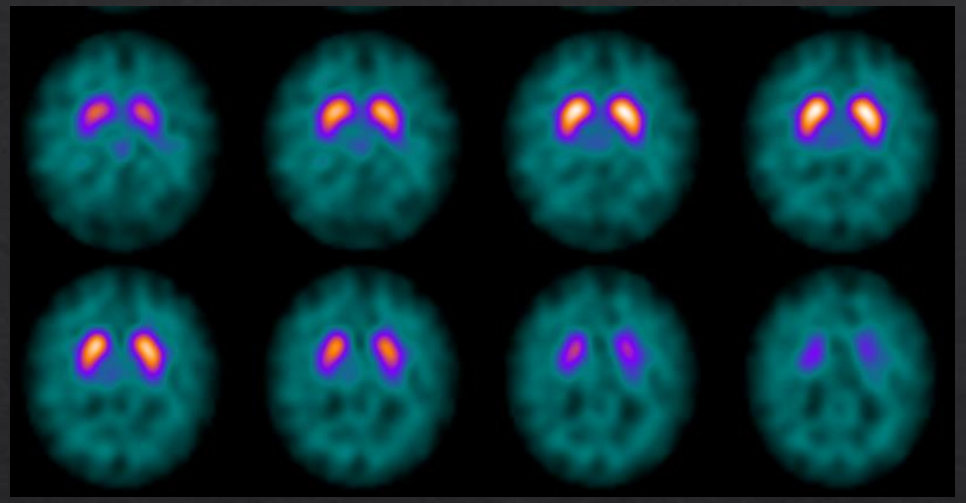


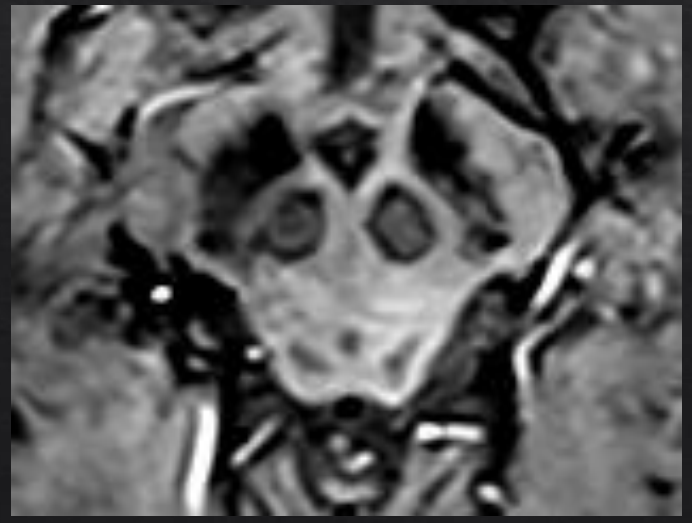


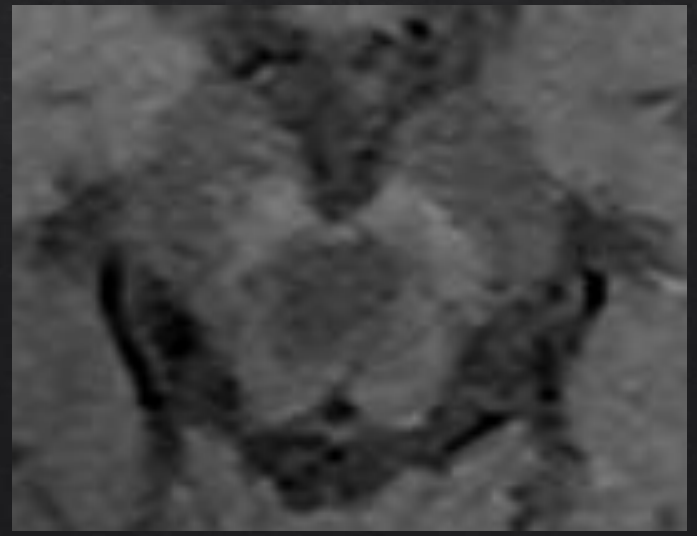
Parkinson vs normal: Nigrosoma/Nmelanina

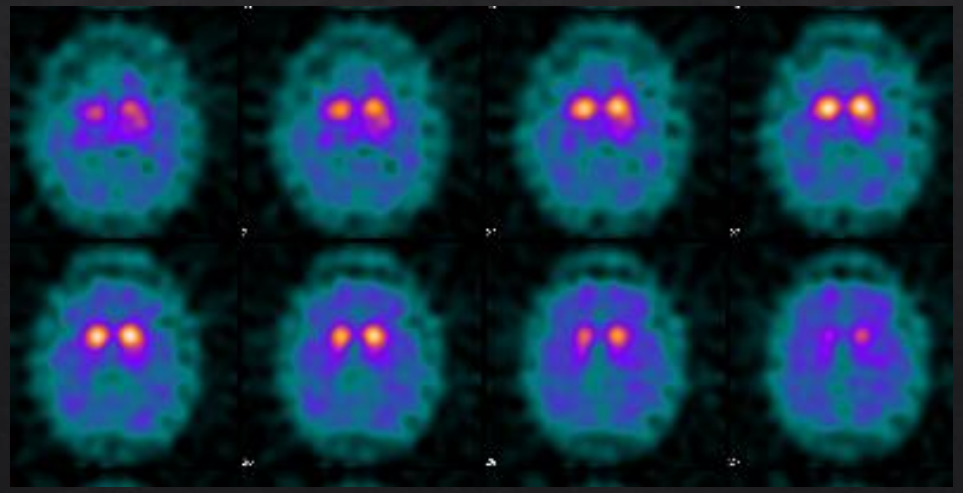


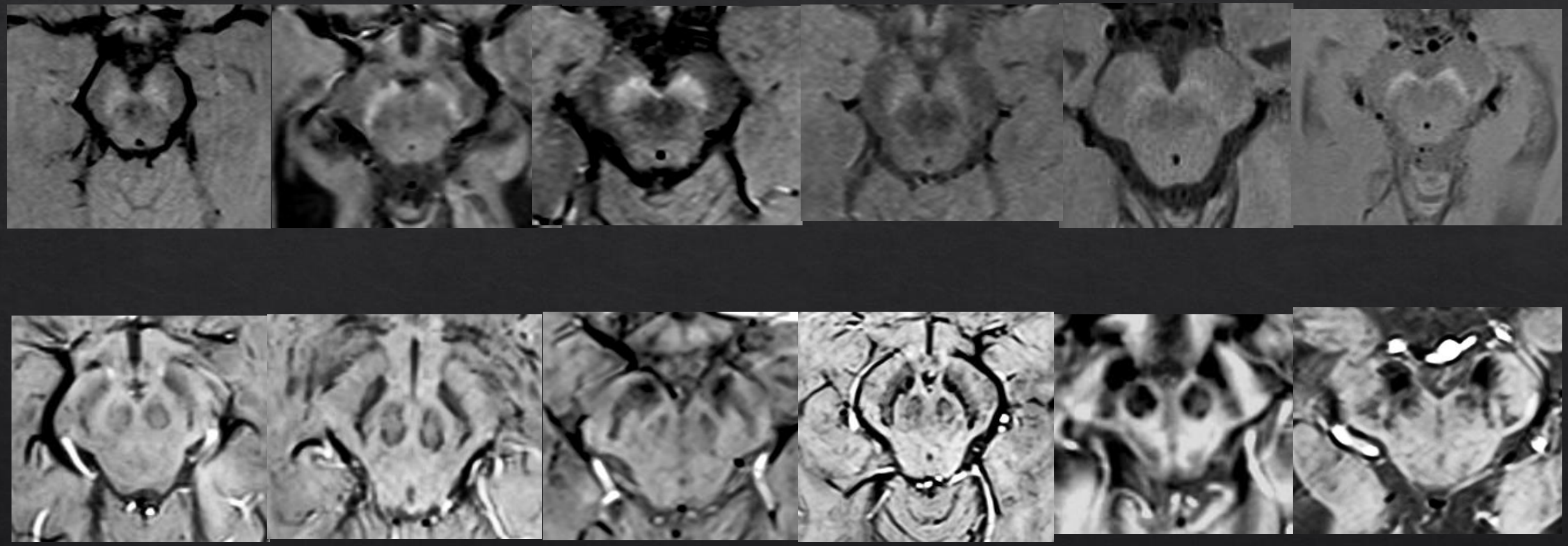












14 a

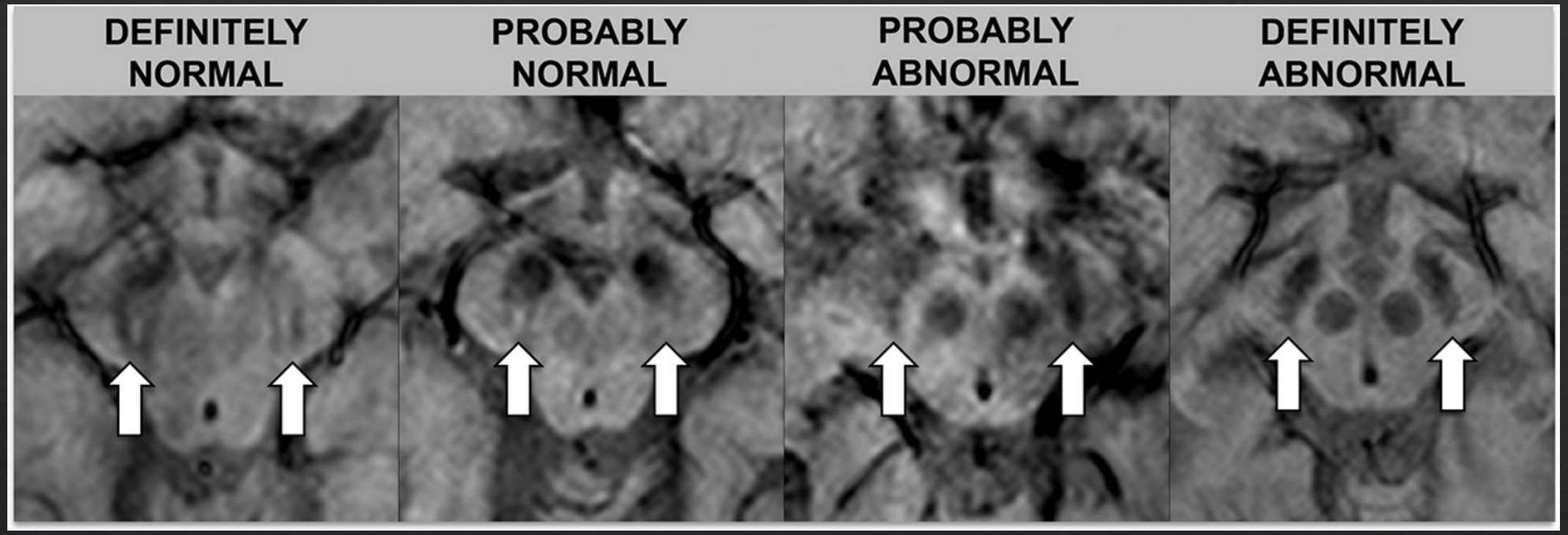
23 a

69 a

EP 39a

EP 70a

TE 63 a



MRI of the Swallow Tail Sign: A Useful Marker in the Diagnosisof Lewy Body Dementia? Ajnr 2017

CONCLUSIONS: The swallow tail sign has diagnostic potential in Lewy body dementia and may be a complement in the diagnostic work-up of this condition.

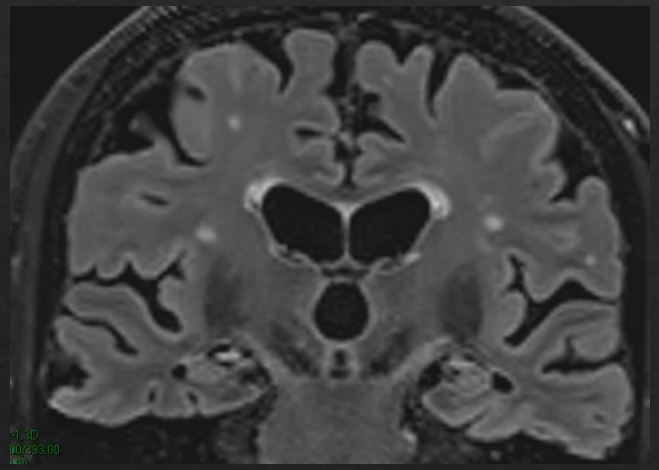
Loss of Swallow Tail Sign on Susceptibility-Weighted Imaging in Dementia with Lewy Bodies. J Alzheimer Dis 2019

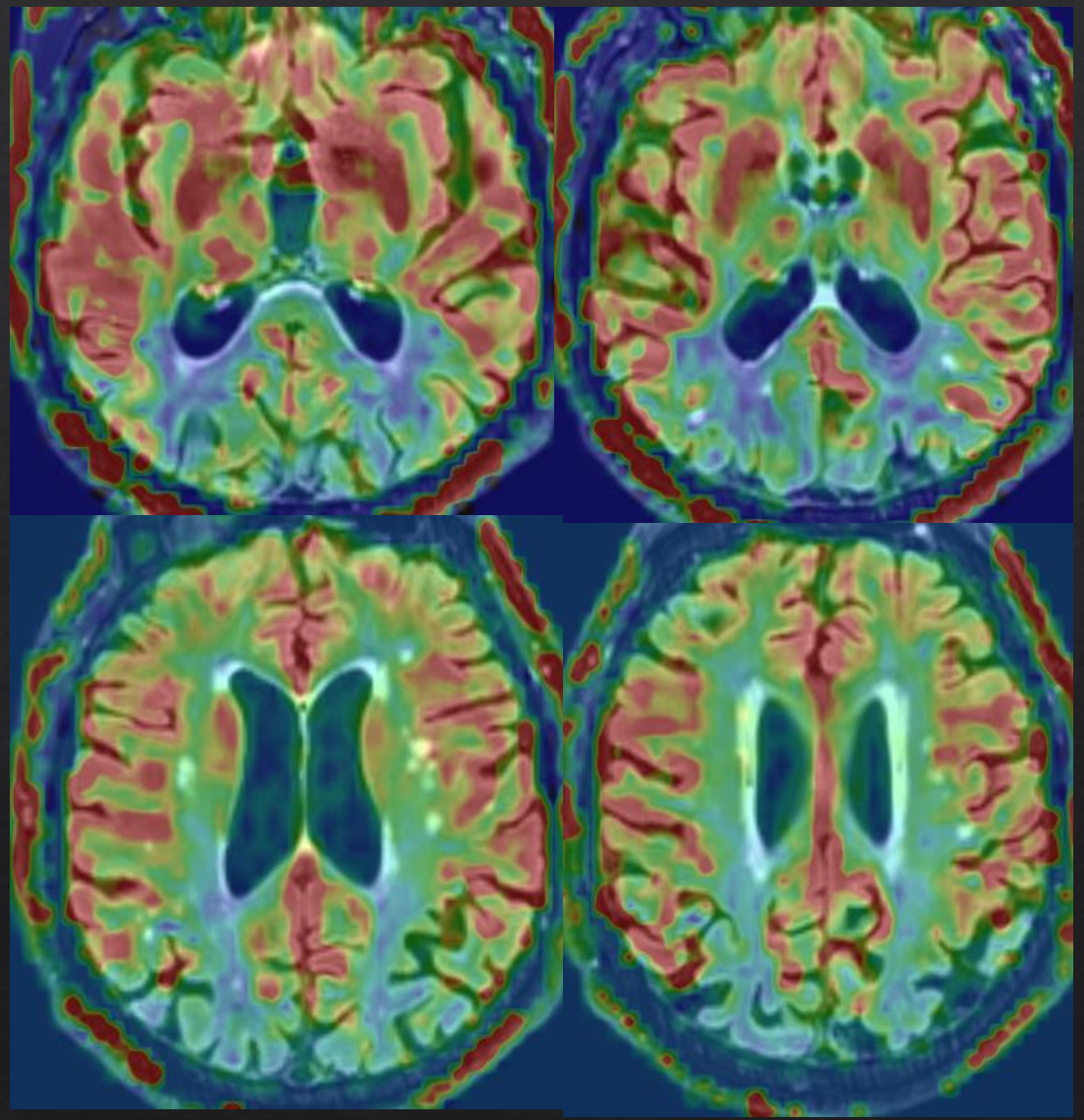
Swallow tail sign loss, especially if bilateral, can be useful for DLB diagnosis.

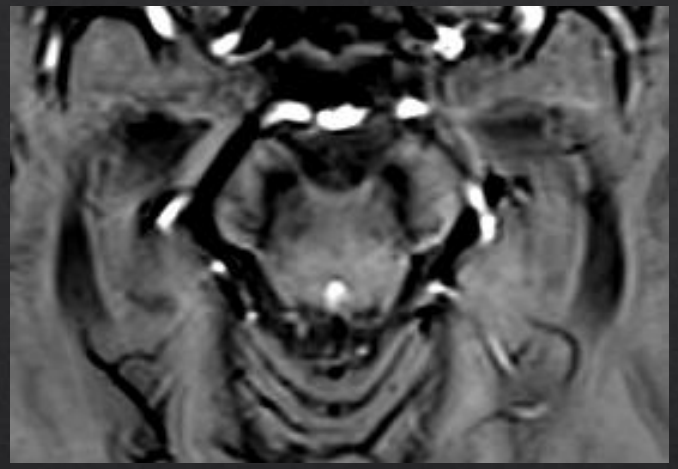
Diagnostic imaging of dementia with Lewy bodies by susceptibility-weighted imaging of nigrosomes versus striatal dopamine transporter single-photon emission computed tomography: a retrospective observational study. Neuroradiology 2017

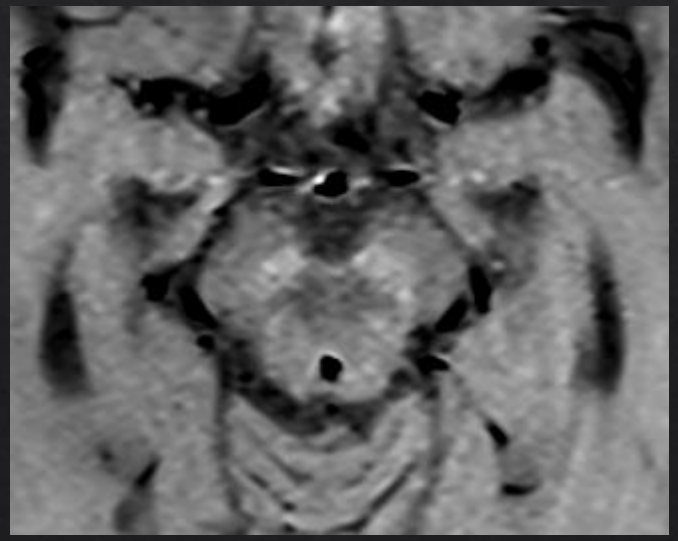
CONCLUSIONS:
SWI nigrosome-1 evaluation was useful in differentiating DLB from AD/a-MCI, with high accuracy. This less invasive and less expensive method is a potential alternative to DaT-SPECT for the diagnosis of DLB.

Lewy: ASL y nigrosoma

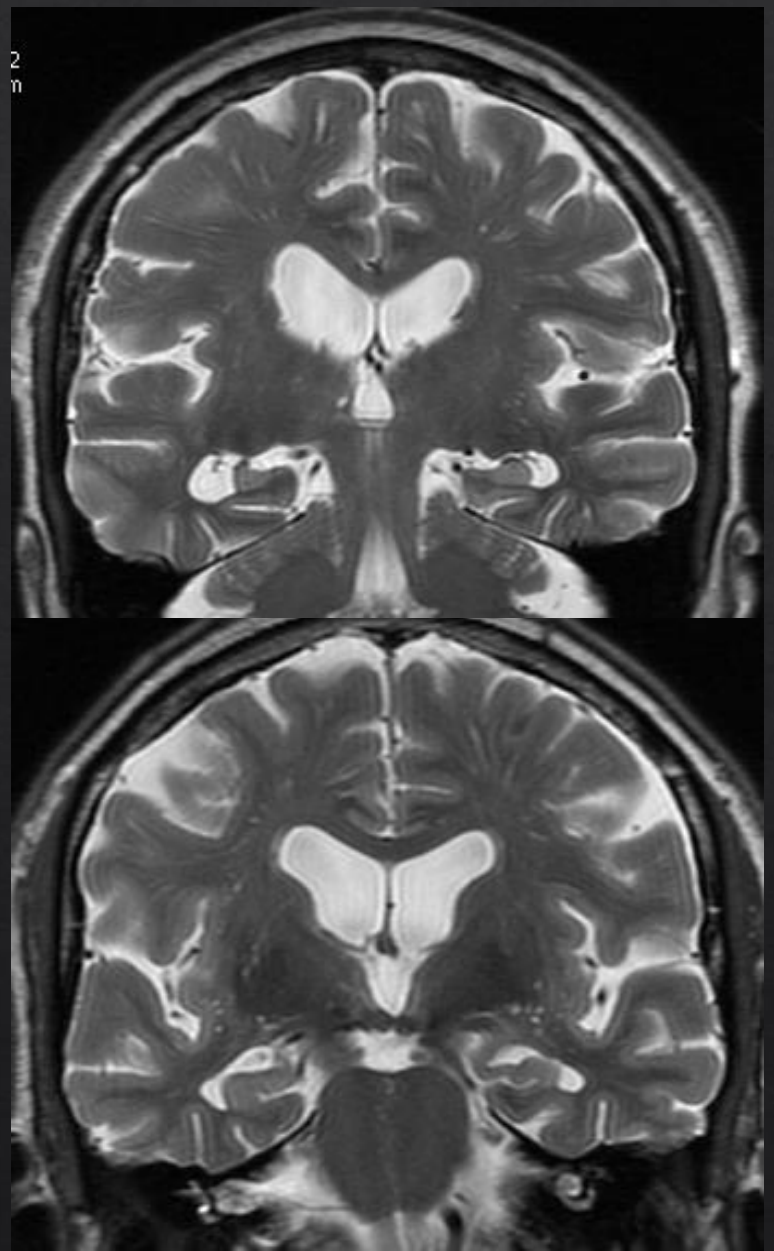


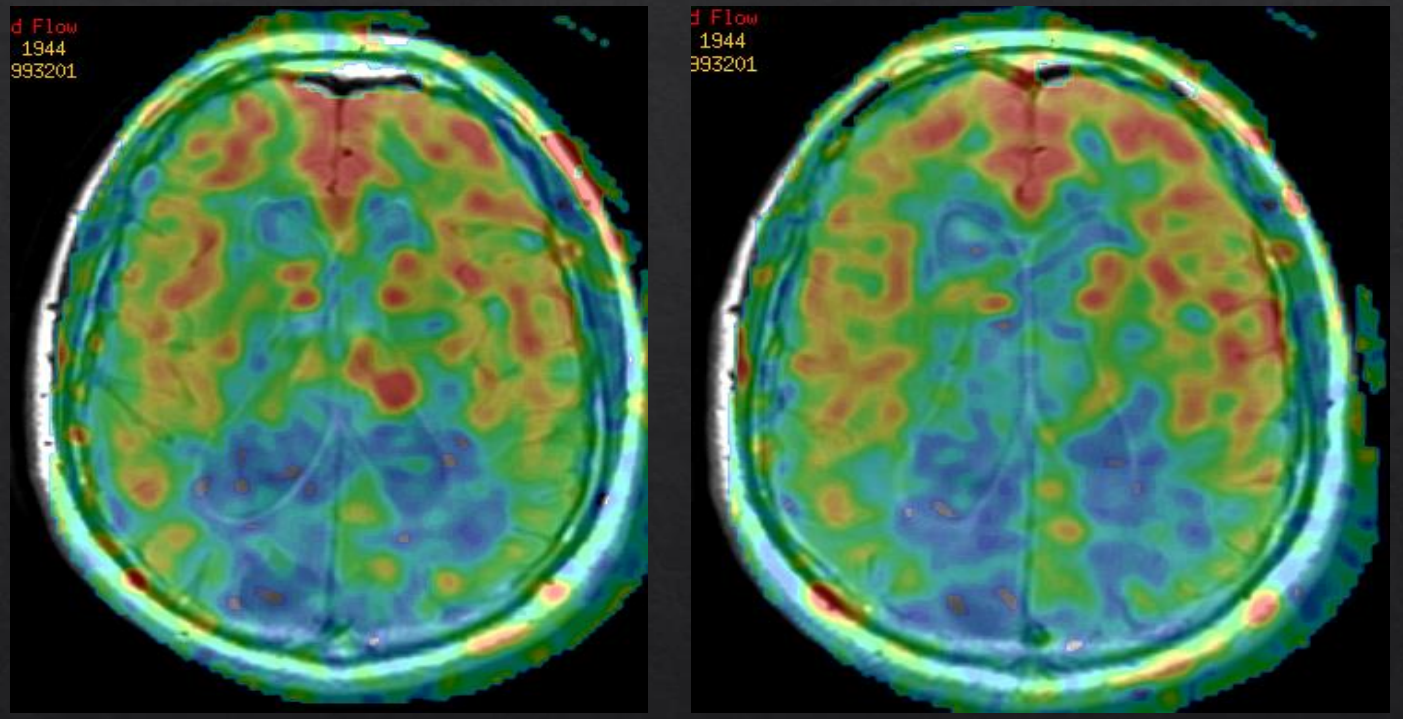






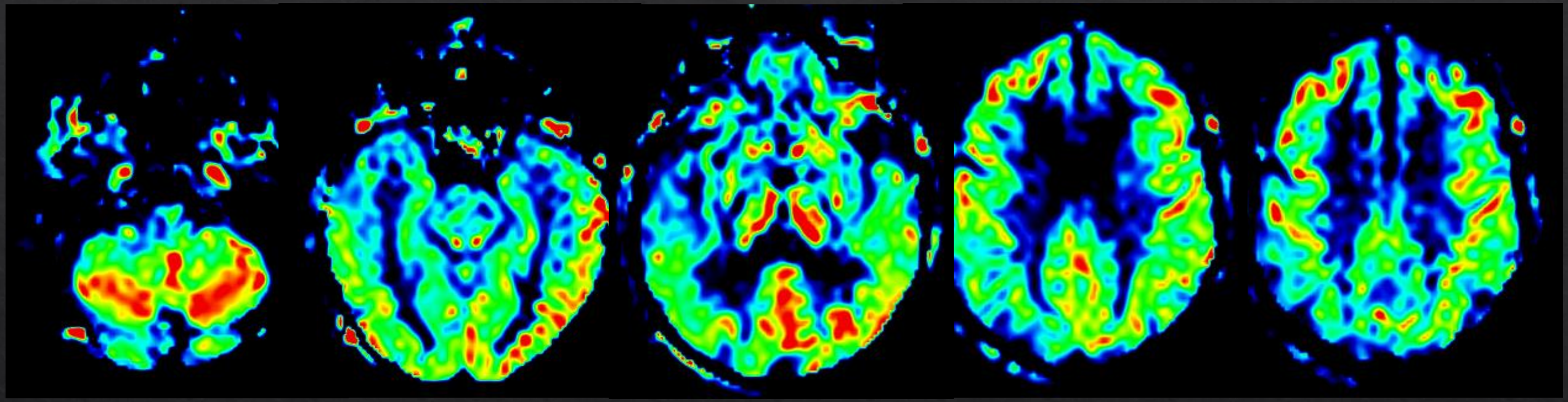
AD: Posterior Cortical Degeneration

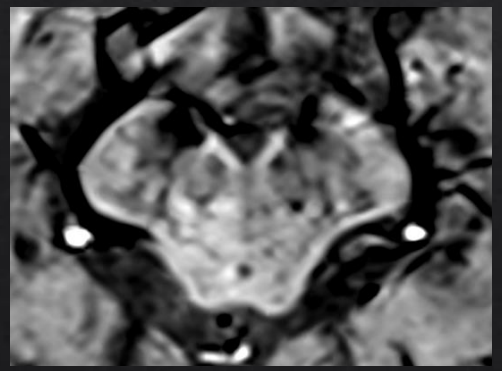


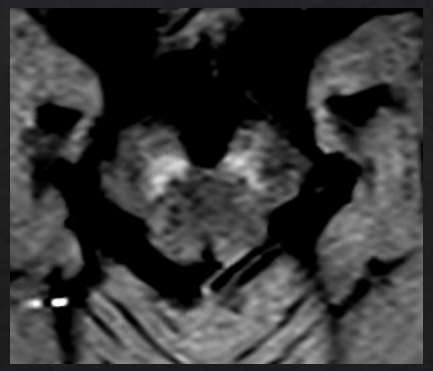


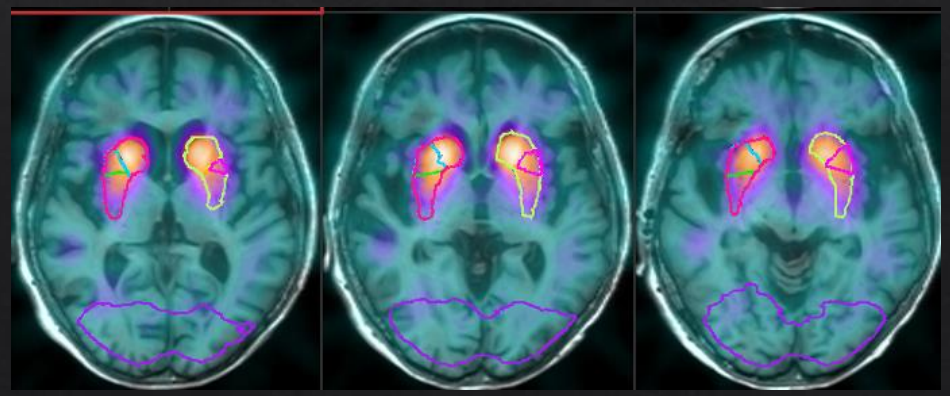
Posterior hypofunction but no Island Sign

DCL fluctuante, trastornos del sueño



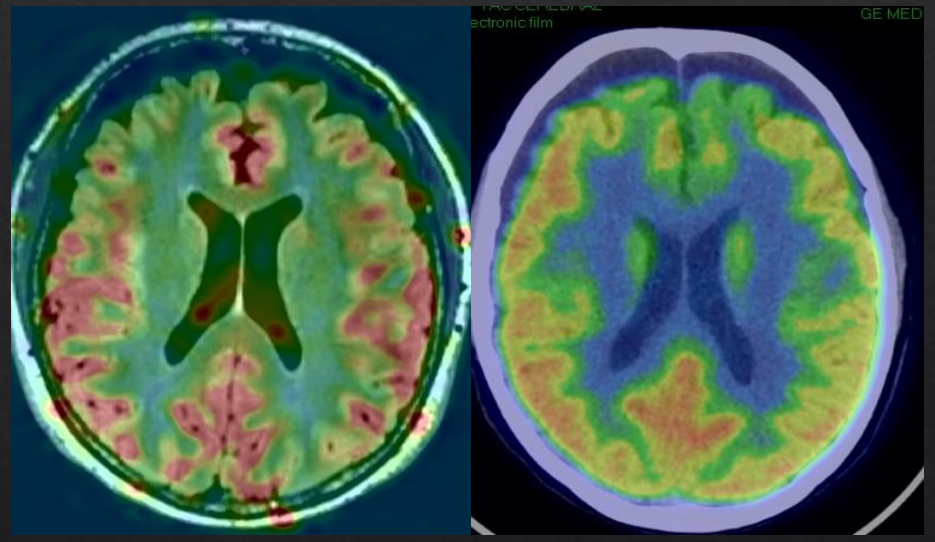




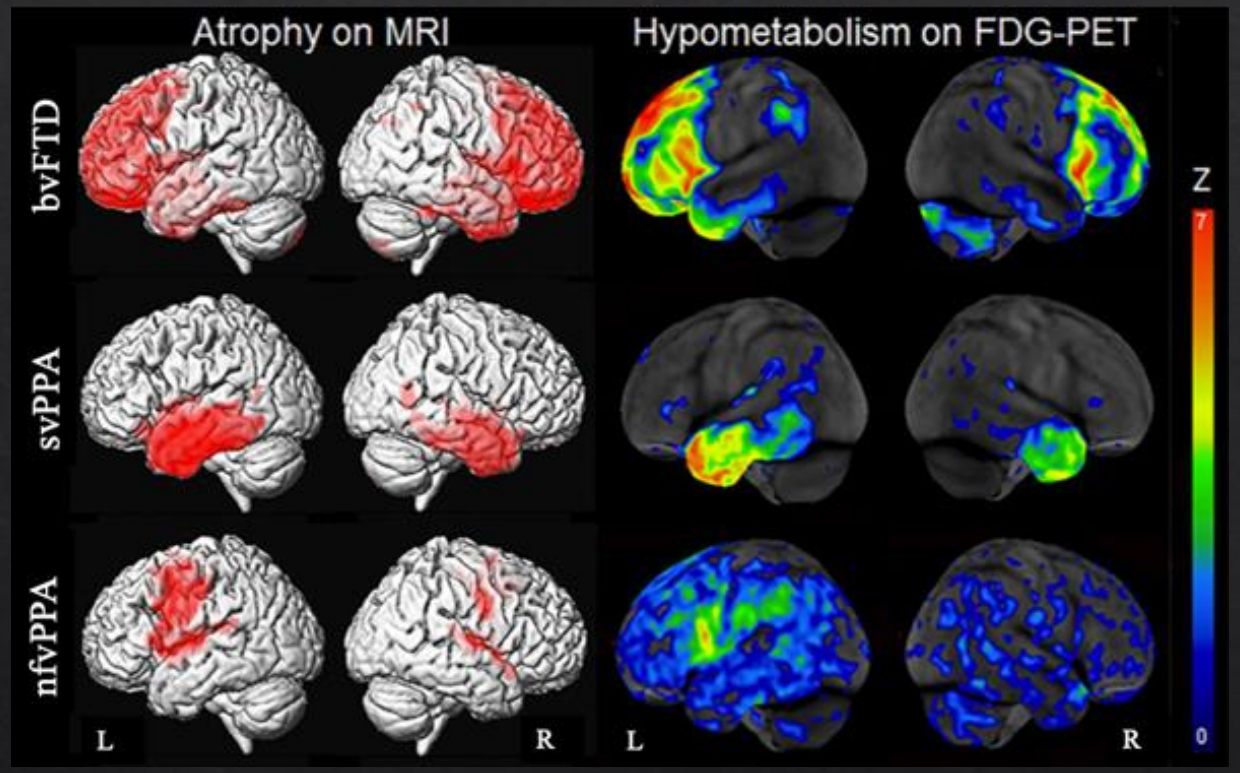


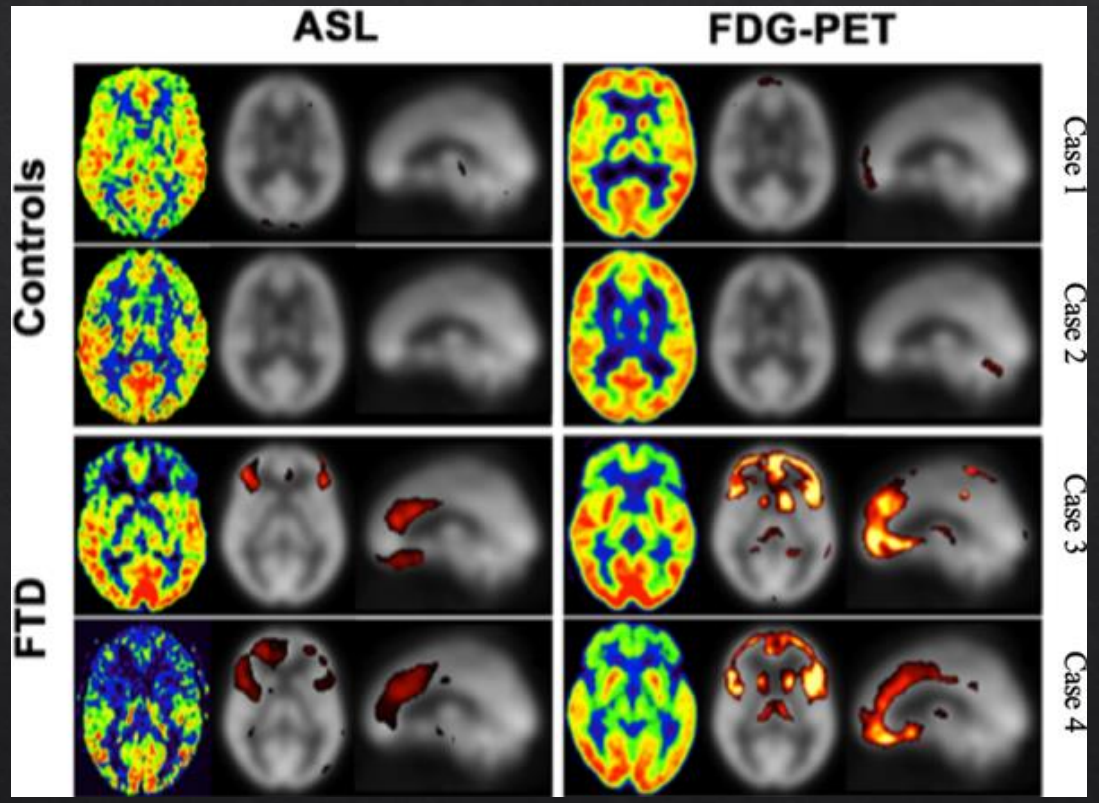
Demencia Fronto-temporal

- Sindrome caracterizado por degeneración frontal/temporal que provoca deterioro progresivo de conducta y/o lenguaje
- 5% de todas las demencias
- 50% en demencia precoz (< 65)
- Frecuente retraso diagnóstico (pat. Psiquiátrica)
  - Exceso de pruebas
  - Stress en entorno familiar
- Variantes de DFT:
  - Conductual: predominio frontal
  - Demencia semántica: predominio temporal (> izdo)
  - Afasia primaria no fluente: predominio Silviano (>izdo)

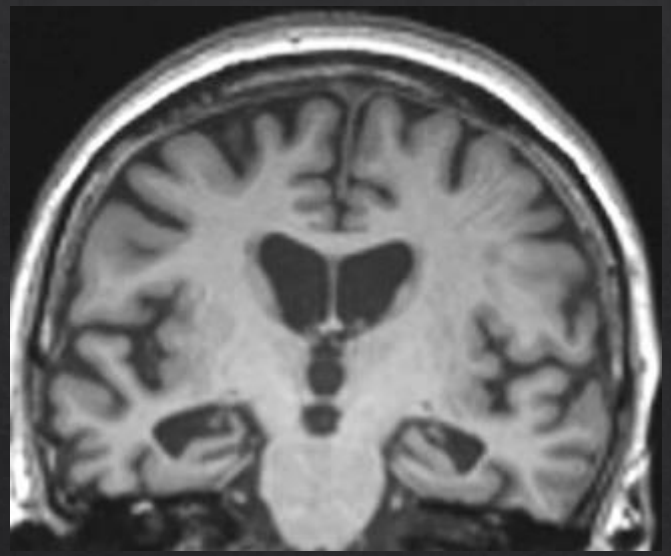


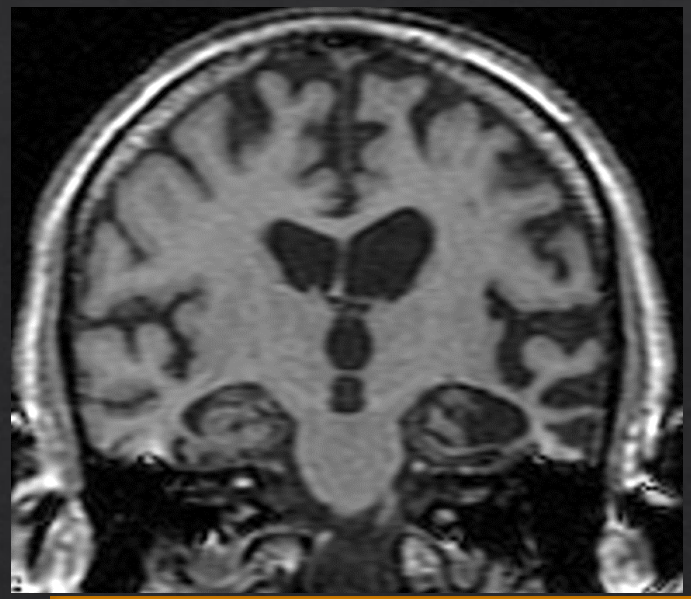
Patrones de afectación estructural y funcional en DFT

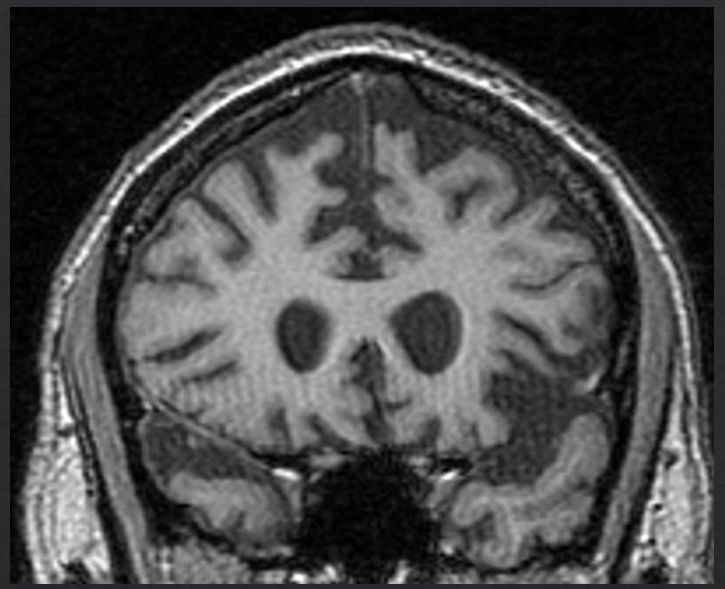


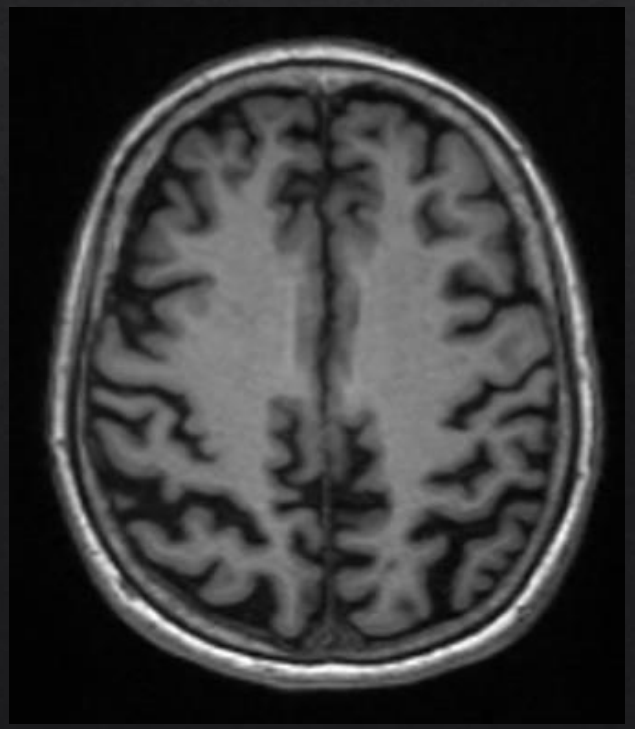


El patrón de neurodegeneración estructural coincide con el funcional pero es menos sensible en fases precoces



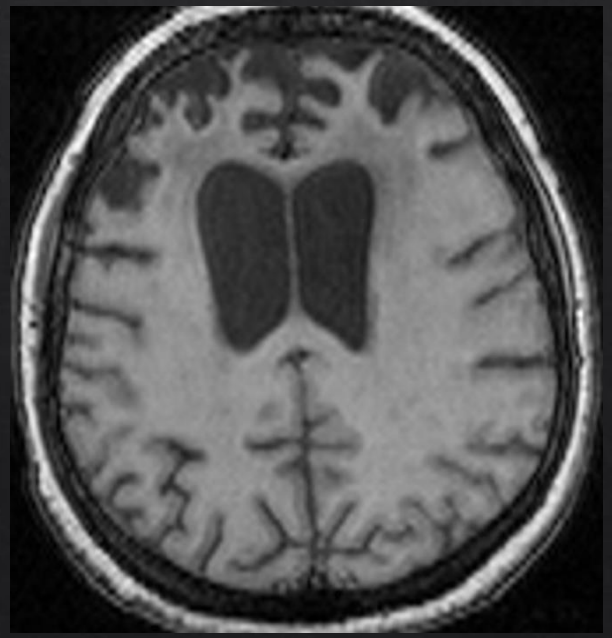




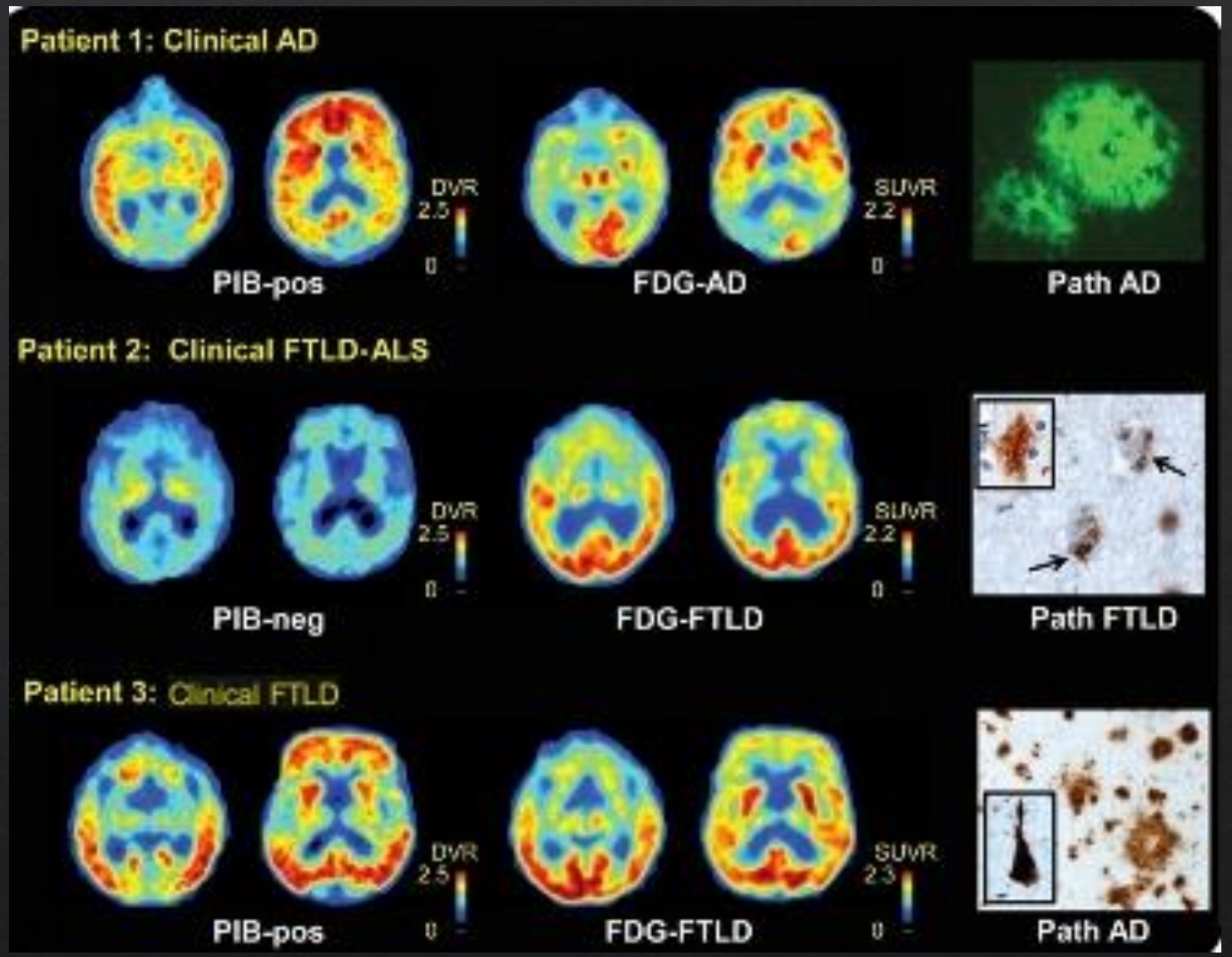


MR findings in Dementia

	AD	VaD	FTLD	Lewi*
Hippocampal atrophy	+++	++	++	-
Temporal atrophy	++	+	+++	-
Frontal atrophy	-	+	+++	-
Parietal atrophy	++	+	-	-
Lacunes	-	+++	-	-
WML's	-	+++	-	-
Strategic infarcts	-	+++	-	-

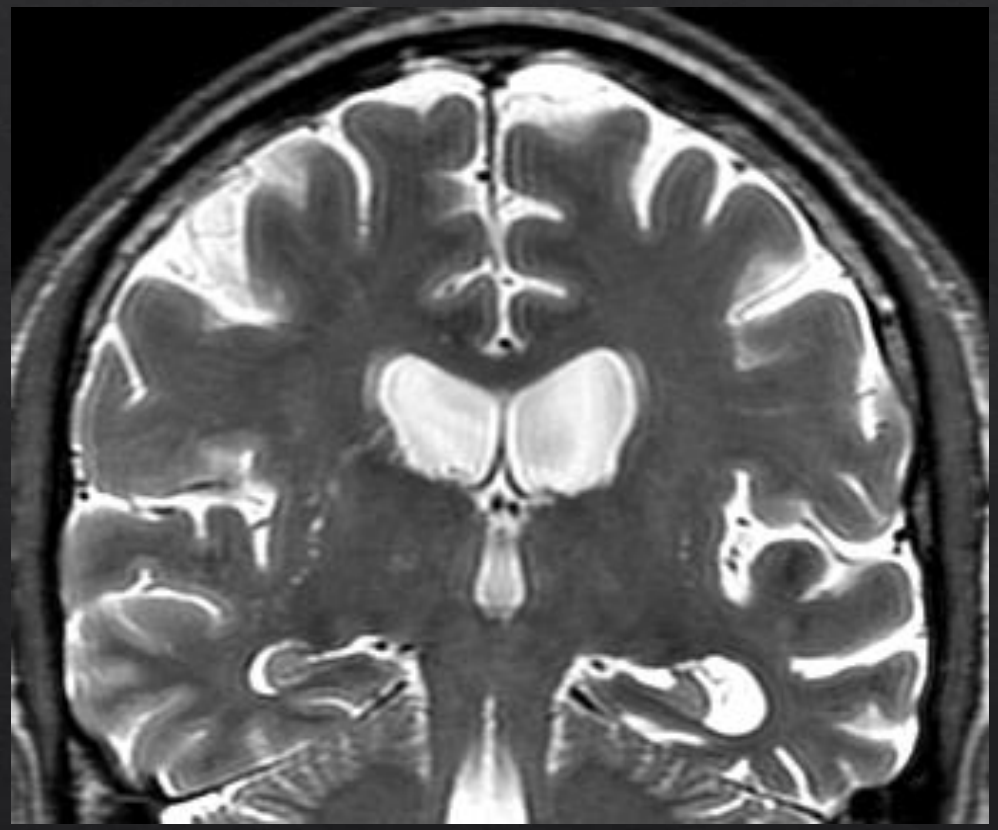


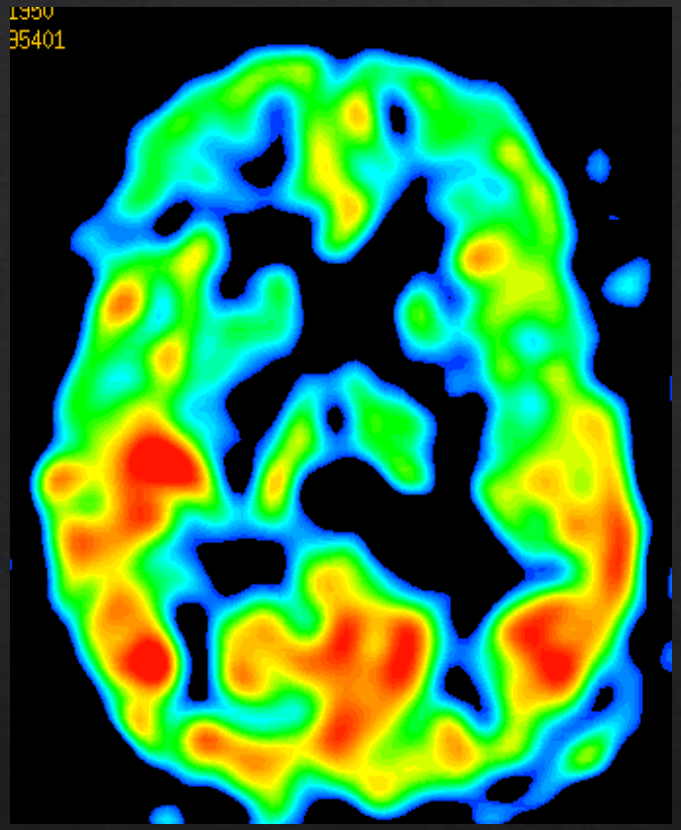
Diagnóstico diferencial con EA



El diagnóstico de EA precisa confirmar marcador A-T

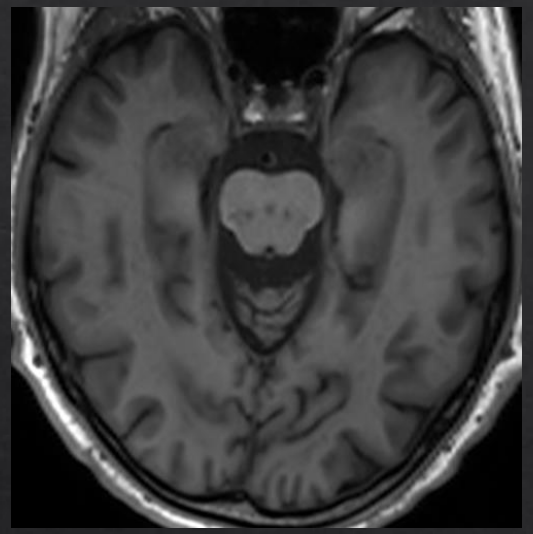
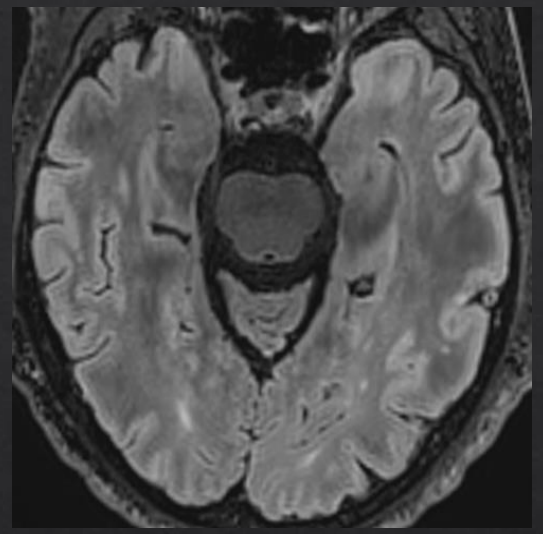
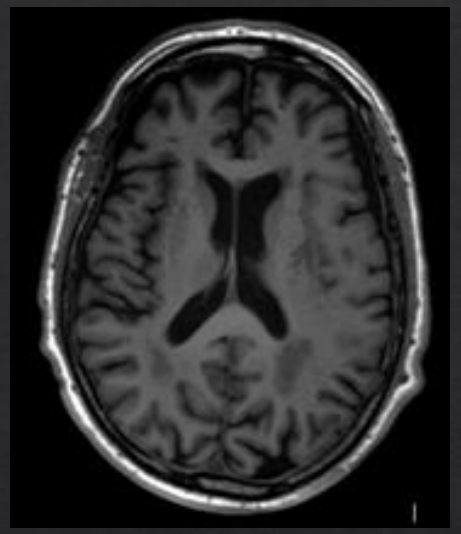
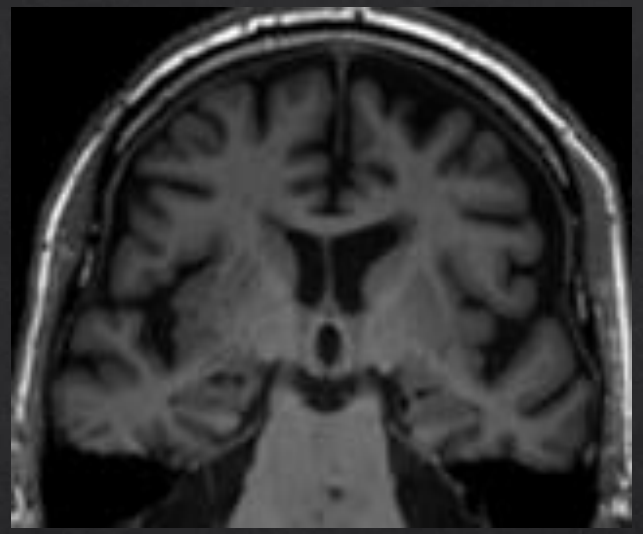
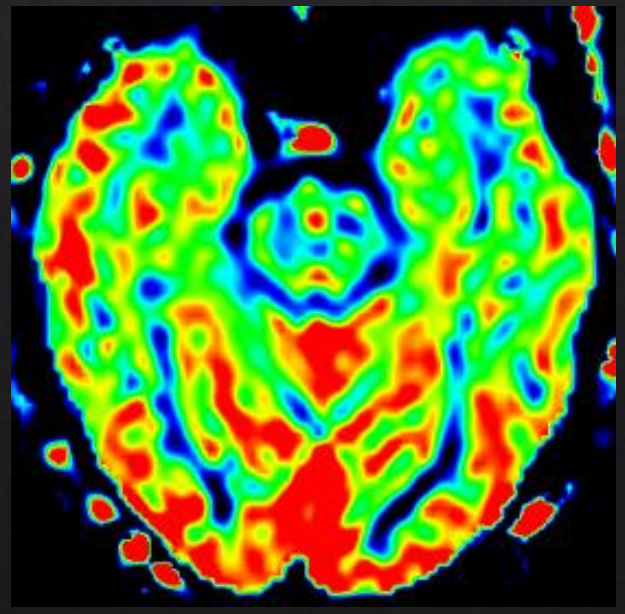
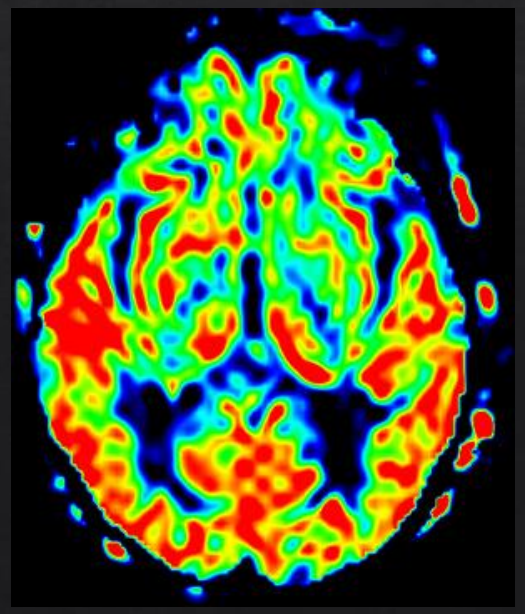
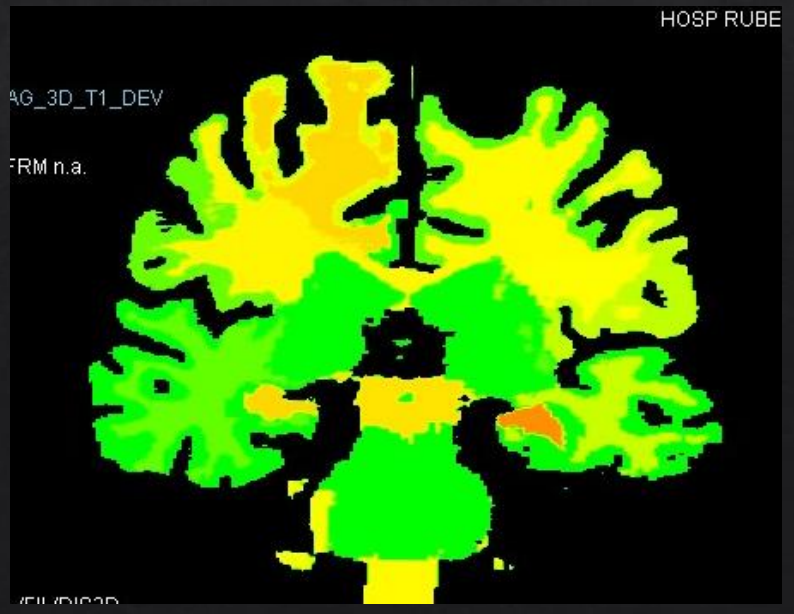
Utilidad del estudio funcional

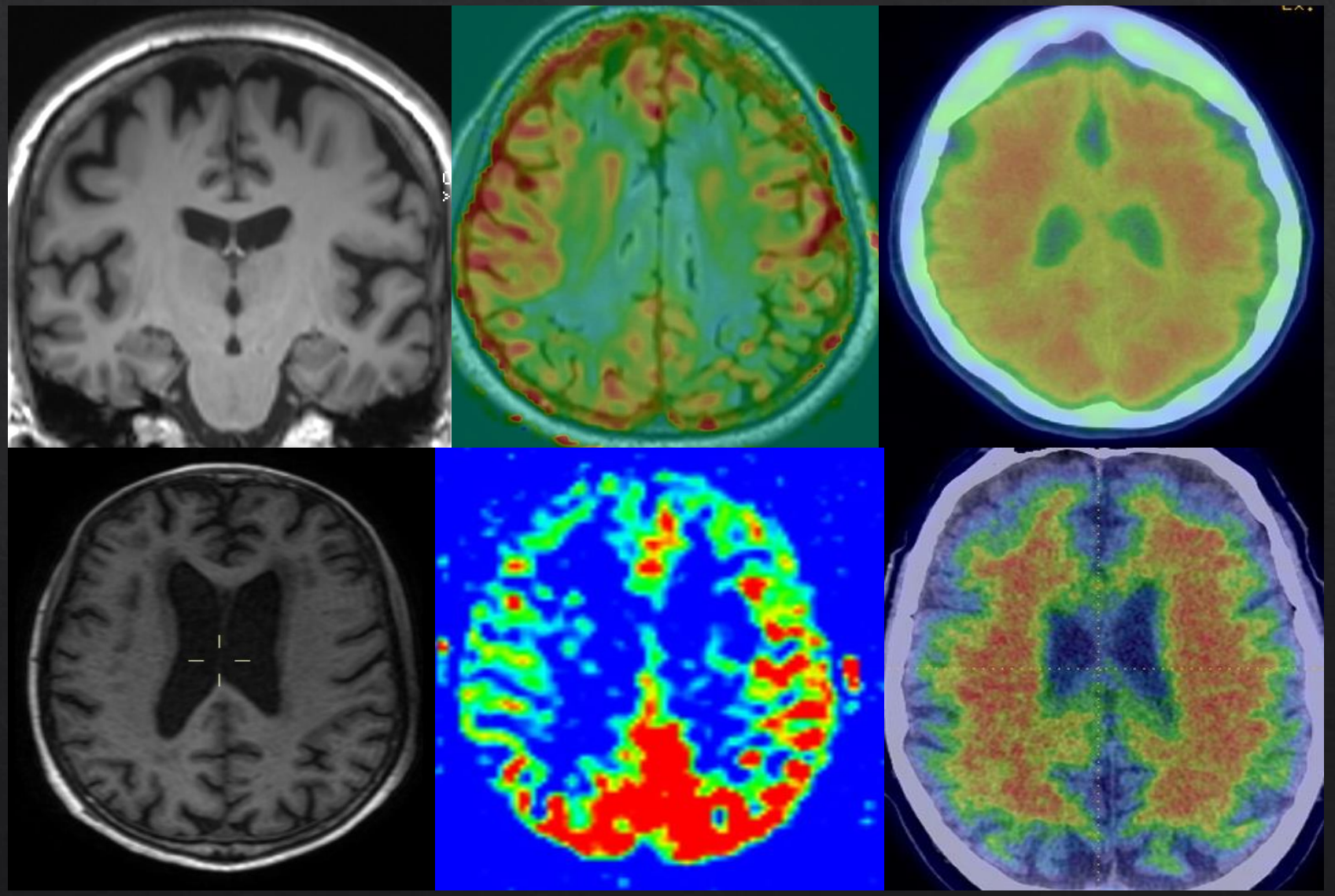




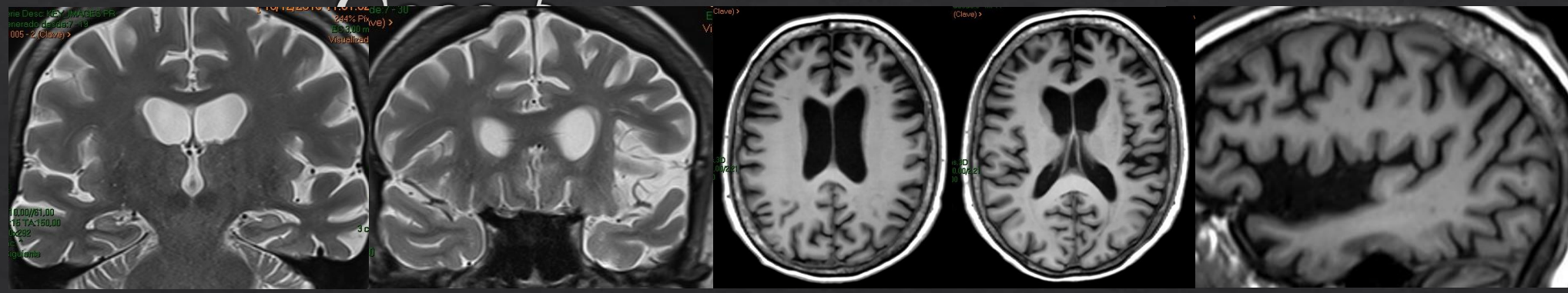
ASL: aumenta la certeza de proceso degenerativo y ayuda a definir patrón de neurodegeneración

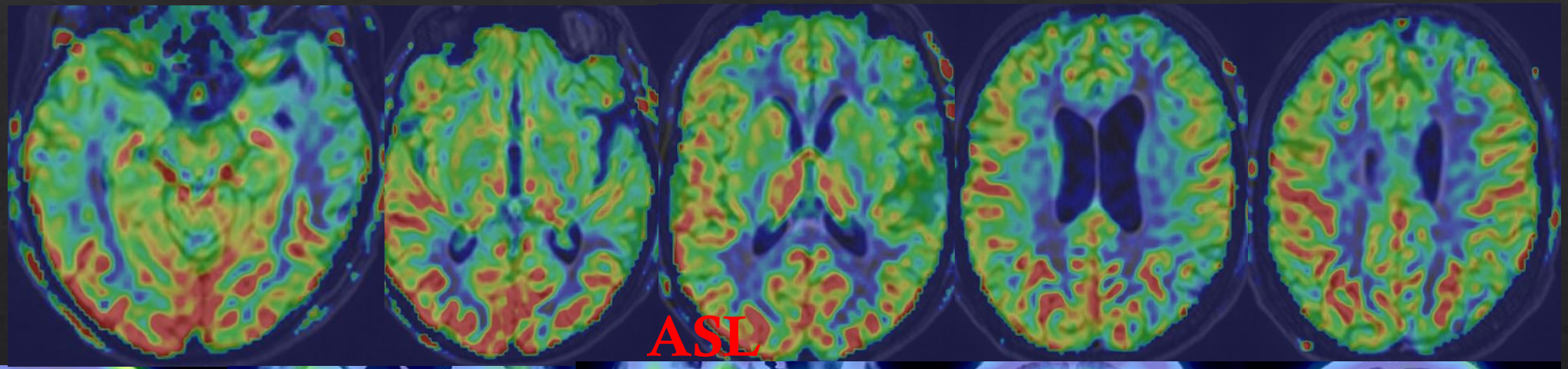
DCL, alteración de conducta

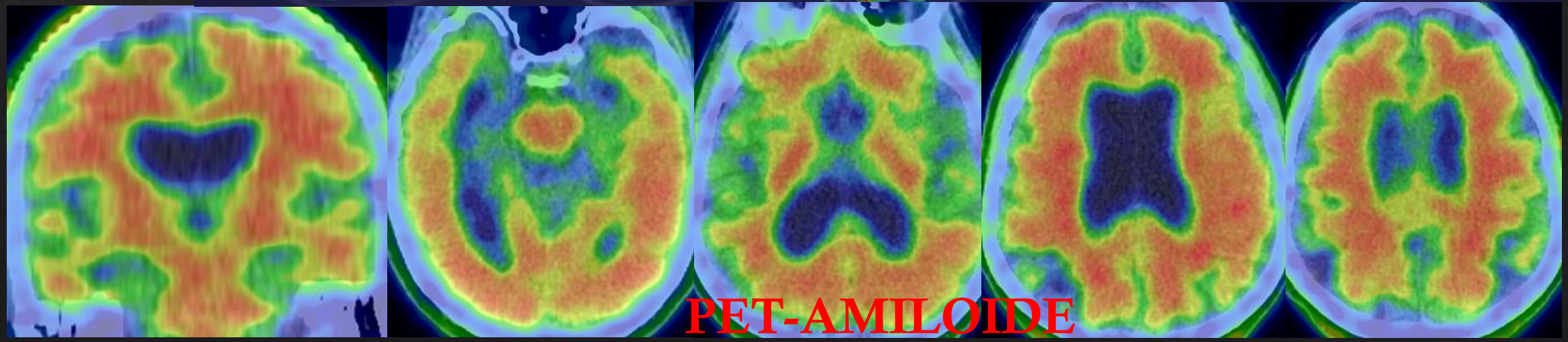










Mujer, 59 años
Deterioro progresivo del lenguaje con predominio de anomia; comprensión conservada
Apatía/agitación







EA: variante logopénica

- Hasta 30% de EA tienen clínica atípica
  - Se caracteriza por no presentar deterioro de memoria
    - Deterioro: Lenguaje/Visuoespacial/Visuoperceptual
  - **Atrofia cortical posterior**
    - Atrofia posterior, hipofunción parieto-occipital
    - Deterioro en Dominio Visual, DDx Lewy (DAT-scan)
  - **Afasia PP: No Fluente, Semántica, Logopénica**
    - No-F, S: la principal causa es la Demencia F-T (Tau/TDP43) (EA 20%)
    - Variante Logopénica: la principal causa es la EA
      - Atrofia de predominio anterior
      - Hipofunción Frontal (PET, SPECT, ASL)
        - Predominio izquierdo
        - Afectación parietal
      - PET-Amiloide: DDx con DFT

Conclusiones

- Las claves diagnósticas de las enfermedades Neurodegenerativas se basan en la VULNERABILIDAD SELECTIVA y se sustentan mediante BIOMARCADORES
  - La imagen funcional ayuda a confirmar (N) cuando la imagen estructural no es concluyente
  - No hay que olvidar los patrones atípicos y mixtos
    - Se necesitan marcadores específicos (A-T)
- El ÉXITO del tratamiento se basa en el diagnóstico PRECOZ y la PREVENCION
  - Marcadores IMAGEN/LCR
  - Marcadores en PLASMA?