MR Imaging of Dementia

Prof. Dr Alexandre KRAINIK
University Hospital of GRENOBLE
FRANCE

Disclosures

PIXYL

GeodAIsics

Objectifs

- To review the main imaging-detectable causes of dementia
- To understand the role of imaging in the management of neurodegenerative diseases
- To discuss the strengths and limitations of imaging

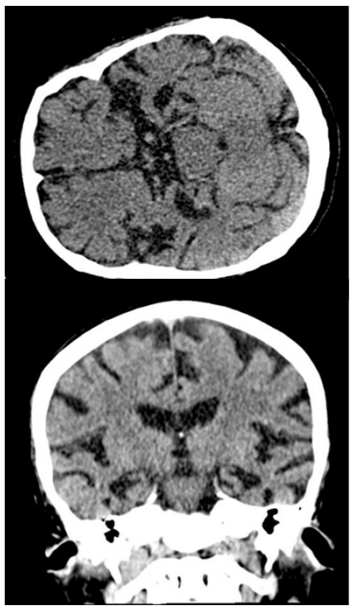
Definition

Prevalence
1M in France
Increases with age
Up to 25% after 85y

- Dementia is a **clinical diagnosis**
- **Progressive** cognitive decline (>6M)
- D+: Cognitive disorders uni/multidomain (MMSE)
  - **Memory** (temporal, hippocampus)
  - Objects and faces **recognition** (temporal, occipital)
  - **Language** (perisylvian)
  - Motor and visuo-constructives **praxis** (parietal)
  - **Dysexecutive sd**: planification, attention, reasoning, judgment, flexibility (frontal)
- Dsev: Loss of autonomy and social functioning (CDR)
- DD: Depression, Confusion (acute delirium)

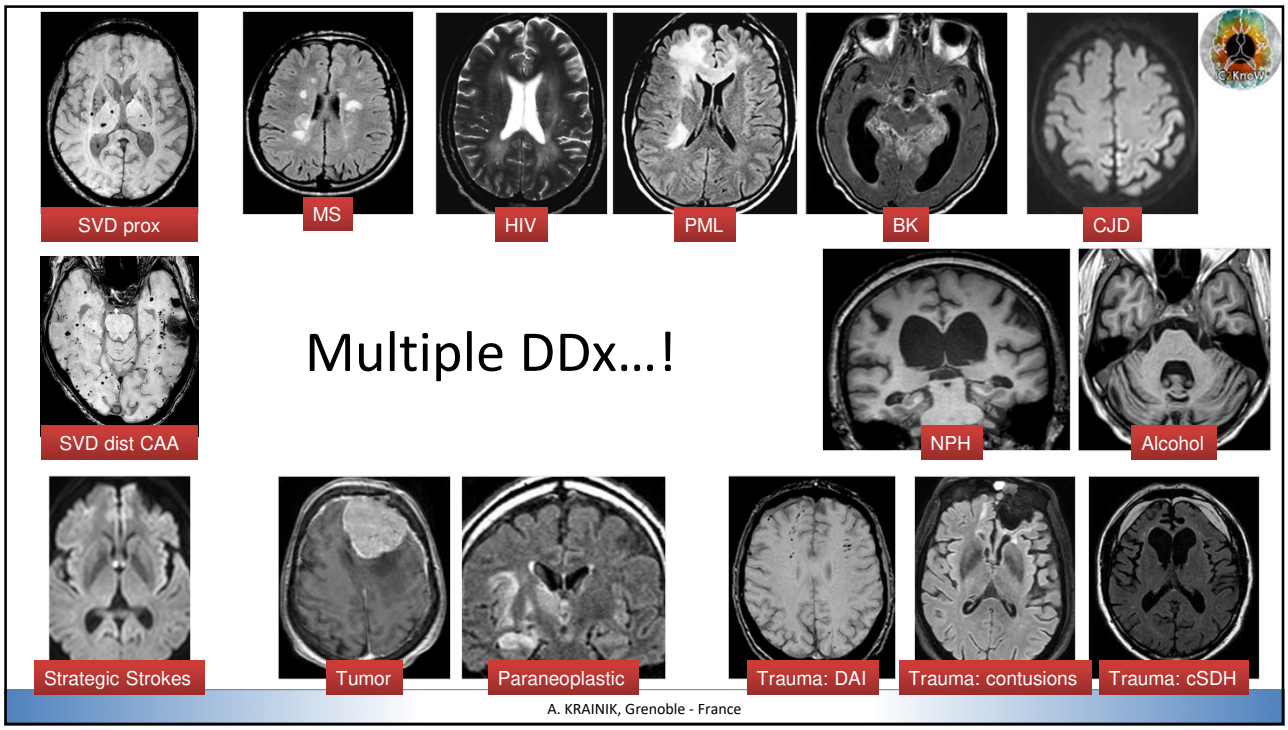
Role of radiologist

- **To collect medical information**: Hx, cognitive decline (domains), atypical features, extrapyr. sd neuropsychological examination; paraclinical data (biology, prior imaging, …)
- **To select the appropriate imaging modality** (CT/MRI)
- **To define and adapt imaging protocols incl. contrast administration** (acquisition and post-processing, MPR)
- **To produce a structured and precise report**
- **To explain results** to the patient and caregivers, to the referring physician



Etiologies of dementia syndrome

- **Variant & Malformative**
- **Vascular**: art, cap, vein, hemato
- **Infection**: vir, bact, fung, par, prions
- **Inflammatory**: MS & Systemic dis.
- **Tumor**: prim, sec, paraneo
- **Trauma**: ext, iatro
- **Toxic**: ext (AODs), iatro
- **Metabolic:** NBIA, hepatic encephalopathy, vit B1 deficiency…
- **Dysfonction:** NPH
- **Degenerative** (***aka*** **proteinopathies)**



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Dementia pies

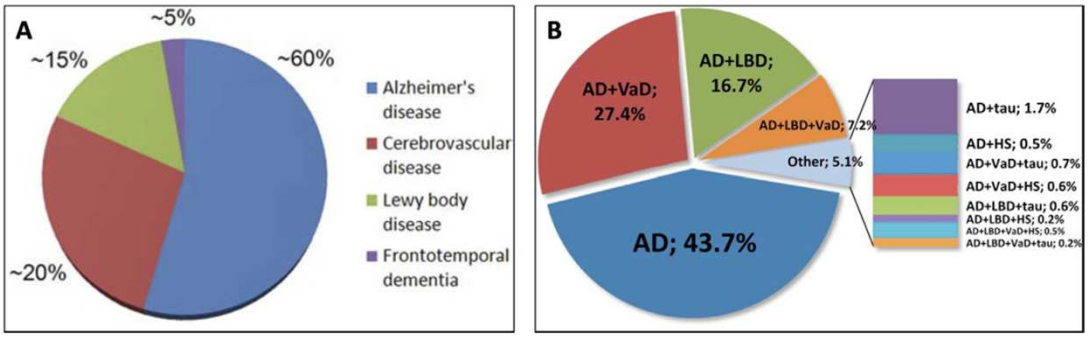


Figure 5: **(A)** Pie chart shows the classic distribution of dementia types in a memory clinic setting, where most cases (60%) are Alzheimer disease (AD). Although AD is attributed to the majority of cases, 40% are not AD. Reprinted, with permission, from reference 32. **(B)** Pie chart shows, according to recent studies, that within the AD group, less than half of cases are isolated AD, while more than half of cases are various combinations of mixed pathologies that include AD. HS = hippocampal sclerosis, LBD = Lewy body dementia, VaD = vascular dementia. Reprinted, under a CC BY license, from reference 33.

Haller et al. *Radiology 2023*

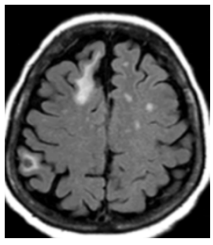
Besides DDx,
MRI has to assess abnormalities related to Vascular diseases & Proteinopathies

Vascular dementia

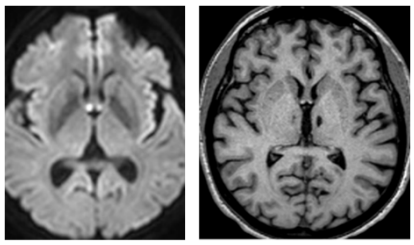
Arterial diseases >100µ

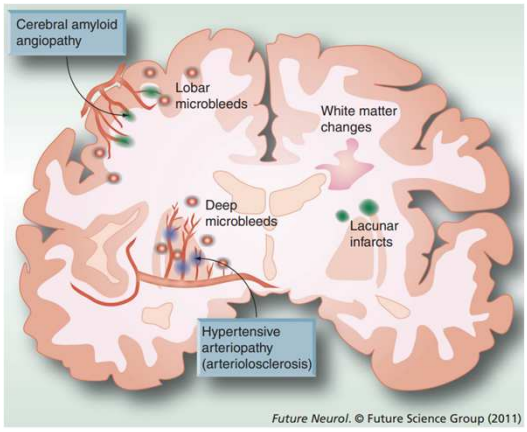
Arteriolar diseases <100µ

Multiple strokes



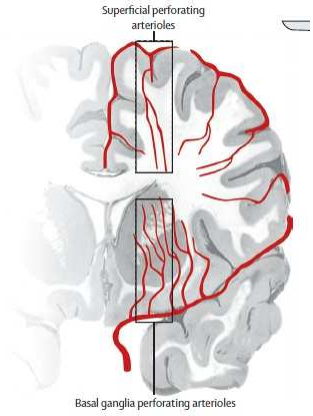
Strategical stroke





Charamidou & Werring *Future Neurol 2011*

Small Vessels Diseases



Wardlaw et al. *Lancet Neurol 2013*

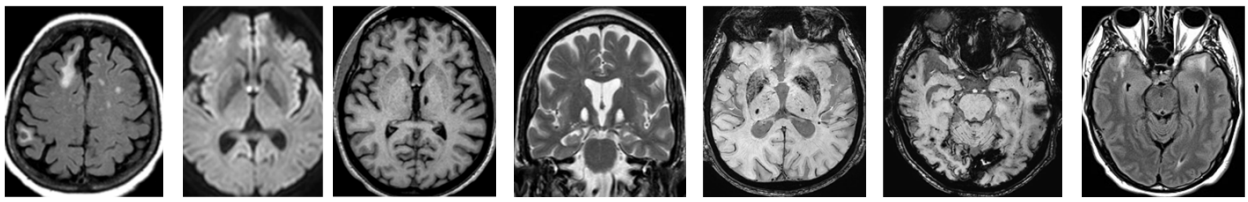
	Arteriolosclerosis	CAA
Location	**Proximal**	**Distal**
Microbleeds	Deep	Superficial
Hematoma	Deep	Lobar
S Siderosis	Uncommon	Common
White matter HST2*	Deep	Subcortical
EPVS	Deep	Subcortical
Microinfarct	Deep	Cortical, Subcortical

***severity with simplified Fazekas's severity scale**

CADASIL

Vascular lesional burden

Multiple strokes | **Strategic stroke** | **Anoxia** | **Arteriolo sclerosis** | **CAA** | **CADASIL**



See lecture on Vascular dementia

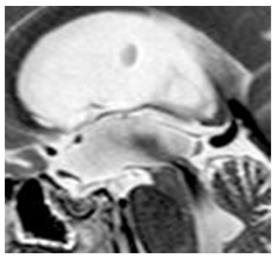
DYSFONCTION: Normal Pressure Hydrocephalus

- Secondary NPH (50%)
  - Hx SAH, meningitis…
  - Extraventricular obstructive hydrocephalus
    - Arachnoid granulations dysfunction
- Primary NPH (50%)
  - No Hx
  - Supposed glymphatic syst. disorder
    - Impaired Amyloid, Tau … clearance

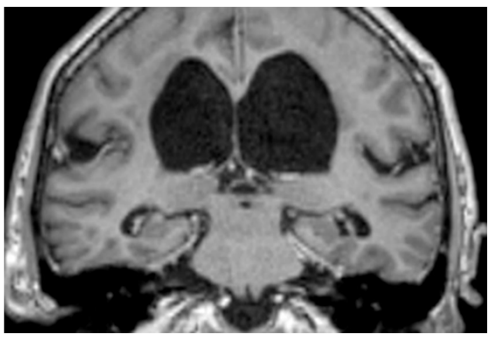
- Clinical symptoms
  - Gait disturbance
  - Urinary incontinence
  - Cognitive impairment

- TTT
  - Drainage, shunt

DYSFONCTION: NPH



- **Ventricular enlargment > SAS**
  - Except lateral sulci
- **No ICH+++**
  - No perimesencephalic SAS narrowing
- **Obstructive:** acute callosal angle
- **Communicating**
  - Aqueductal flow artifact
- **Chronic**
  - No or few transependymal CSF resorption



THM 1

- Dementia is a clinical diagnosis; imaging supports etiological assessment
- Contrast enhancement is not required in the absence of systemic disease
- Non-contrast CT (+MPR) may be sufficient to rule out surgically treatable causes
- MRI allows more accurate characterization of neurodegenerative disorders with a minimal protocol: 3DT1, 3DFLAIR, DWI, SWI

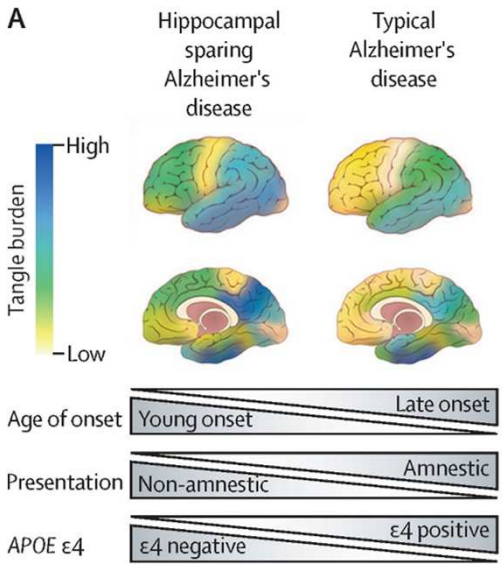
MRI of Alzheimer's Disease

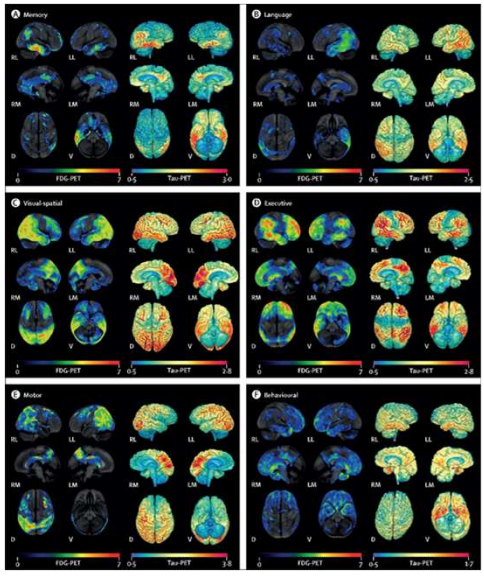
Prof. Dr Alexandre KRAINIK
University Hospital of GRENOBLE
FRANCE

AD Diagnostic *in vivo*

1984 NINCDS-ADRDA criteria	2007-2014 IWG criteria	2018 ATN criteria	2024 IWG criteria
Clinical	Clinical	Clinical	Clinical
Imaging	Imaging	Imaging	Imaging
Biology	Biology	Biology	Biology
Alzheimer's disease **Definite, Probable, Possible**	**Preclinical AD** **Alzheimer's pathology** **Alzheimer's disease**	**A+: Alz pathol changes** **A+/T+: AD** **A+/T+/N+: AD**	**At risk of AD** **Presymptomatic AD** **AD**
McKhann. *Neurology 1984*	Dubois. *Lancet Neurol 2007* Dubois. *Lancet Neurol 2010* Dubois. *Lancet Neurol 2014*	Jack. *Alzheimers Dement 2018*	Dubois *JAMA Neurol 2024* Jack Alzheimers Dement 2018

Clinical and Imaging Diversity





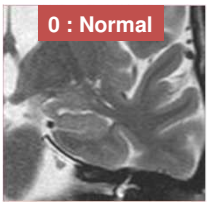
Graff-Radford et al. *Lancet Neurol. 2021*

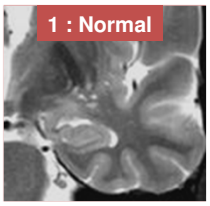
MR Imaging in AD

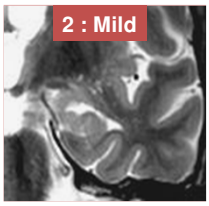
MRI in AD

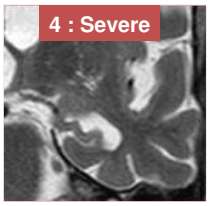
- D+: Regional cerebral atrophy unrelated to civilian age
  - Temporal & hippocampus **(Scheltens's severity scale)**
  - Parietal / Antero-posterior gradient of fronto-parietal atrophy
  - Atypical
- D-: **No grey matter signal abnormality (except vasc)**
  - No nigrosomes loss, No SN neuromelanin loss
  - Except when … DLB association
  - No HS DWI, no abnormal iron accumulation
- Associated features: **Vascular lesions**
  - Stroke, HST2 **(Fazekas)**, EPVS dilation, CMBs, CSS,…
  - Art Prox (NGC, caps), Art Dist (Cortico-sous-cortical), Vein (PeriV)
- **DDx +++**

Hippocampal atrophy (Scheltens 0-4)









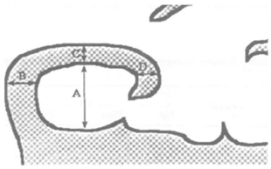


Table 1 Visual rating of medial temporal lobe atrophy

Score	Width of choroid fissure	Width of temporal horn	Height of hippocampal formation
0	N	N	N
1	↑	N	N
2	↑↑	↑	↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

↑ = increase, ↓ = decrease. N = normal.

Scheltens *JNNP 1992*

Parahippocampal atrophy (ERICA)

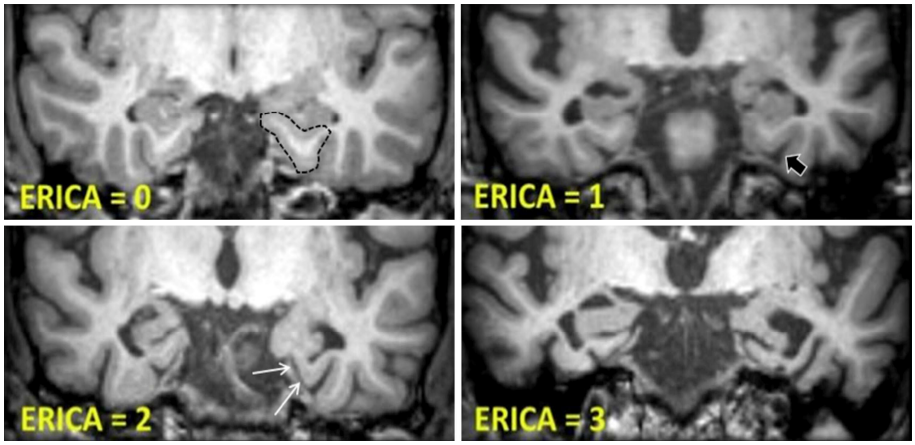
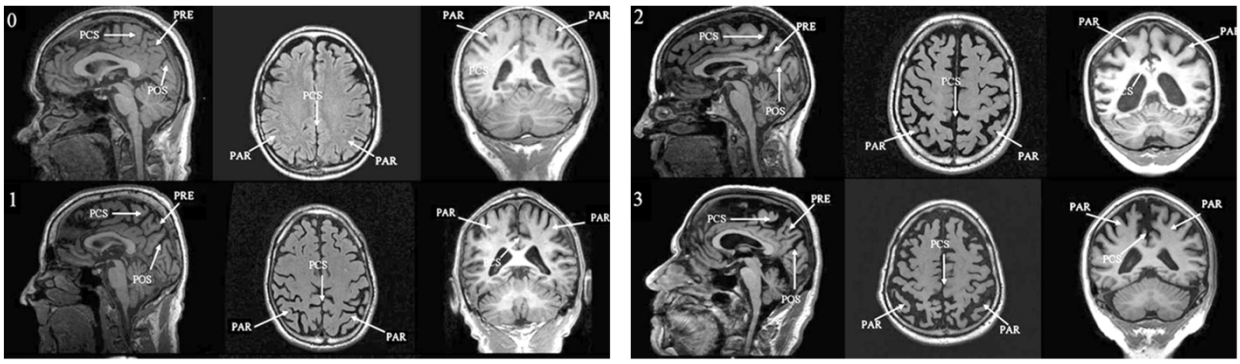


Figure 3: The ERICA score. The visual pattern for entorhinal cortex atrophy was defined as follows: A score of 0 indicated normal volume of the entorhinal cortex and parahippocampal gyrus (marked area); a score of 1, mild atrophy with **widening of the collateral sulcus** (black arrow); a score of 2, moderate atrophy with detachment of the entorhinal cortex from the cerebellar tentorium (the "**tentorial cleft sign**"; white arrows); and a score of 3, pronounced atrophy of the parahippocampal gyrus and a wide cleft between entorhinal cortex and the cerebellar tentorium.

Enkirch *Radiology 2018*

Parietal atrophy

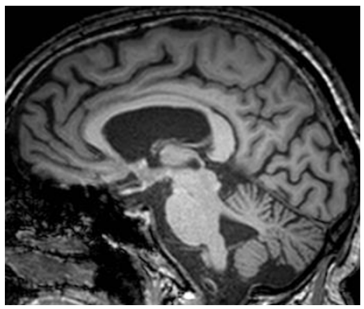


Koedam *Eur Radiol 2011*

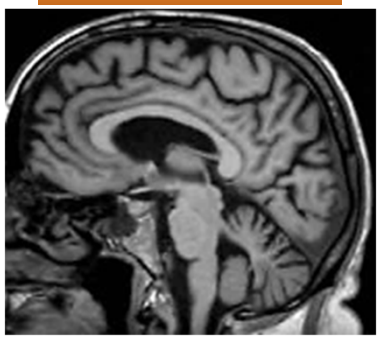
Anteroposterior gradient of frontoparietal atrophy

AD

FPAG Frontal

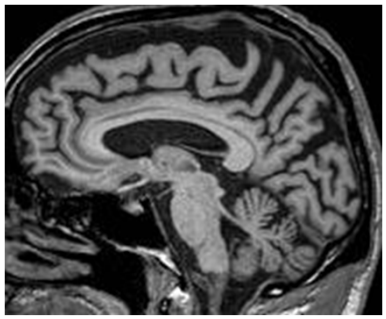


FPAG Ø



WMHST2 Fazekas 2-3

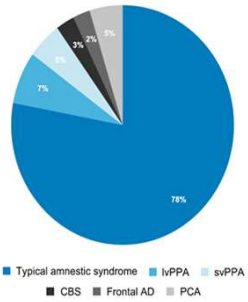
FPAG Parietal

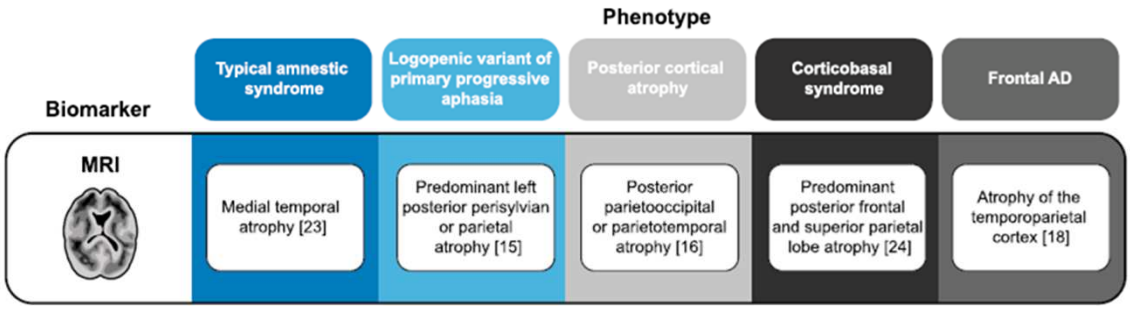


No WMHST2 Fazekas 0-1

Chapuis *Neuroradiology 2016*

Clinical and Imaging Diversity





Dubois *Alz Res 2023*

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GeodAisics

FRANCE 2030

GOUVERNEMENT

bpifrance

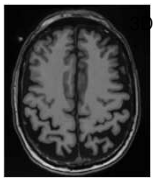
La Région Auvergne-Rhône-Alpes

French Healthcare

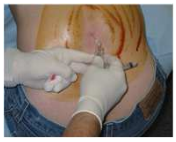
BrainGML®-AD

BRAINGML®-AD: AI SOFTWARE TO DETECT ALZHEIMER

Multimodal learning



T1 WI + Deep Learning
(5000 patients)



CSF Analysis
(1600 patients)

MRI only for inference

Results

3 categories output

AD High risk | **Uncertain** | **AD Low risk**

3 quantitative biomarkers AD's specific
TAU
P TAU 181
Aβ42
Visualize atrophy regions for explanation

GOLD STANDARD FOR TESTING

Post Mortem Brain Autopsy
(400 patients)

GeodAIsics

BRAINGML-AD : TAKE HOME MESSAGES

Early & Accurate diagnostic Integrable into patient worflow after the 1st line exam : MRI

Select patients for Alzheimer treatment

Results in 15 Min, during radiologist appointment

93% Sensibility
85% Specificity
Unique CE AI software to detect Alzheimer

Similar results as true CSF save time, cost and risky testing

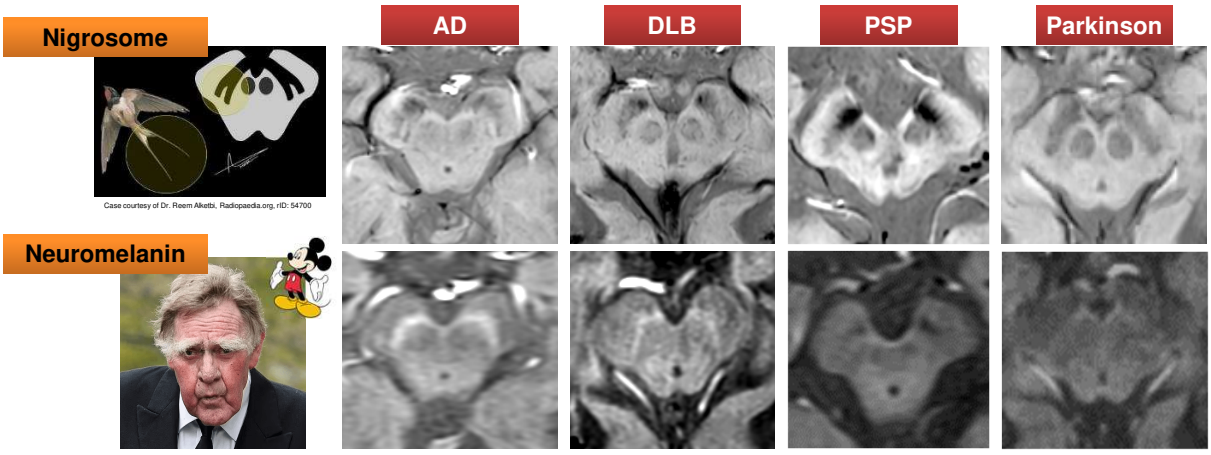
GeodAIsics

Normal Basal Ganglia

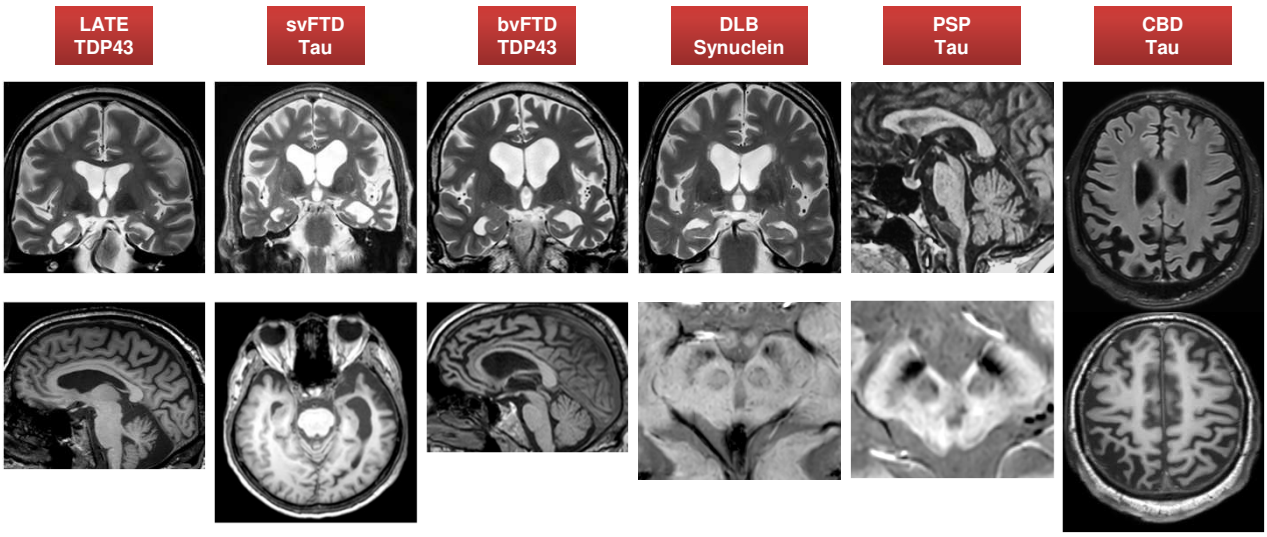
- Abnormal iron or calcification?

Normal Substantia Nigra

- Nigrosomes visibility (N=80%), exc. with DLB (20% et AN 2/3)
- No neuromelanine loss



DDx : Other Proteinopathies



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THM 2: MRI in AD

- MRI in AD is helpful for Diagnostic challenge
  - Differential diagnosis: proteinopathies, other causes of cognitive dis.
  - Associated vascular involvement
  - MRI: comprehensive protocol, exhaustive and standardized description, interpretation with known limitations, direct communication
- MRI in AD is mandatory for Therapeutic challenge
  - Selection for exclusion of patients at risk of ARIA
  - Therapeutic monitoring
  - Work in progress WIP

A. KRAINIK, Grenoble - France

MR Imaging in FTDs

FTDs vs FTLDs

Frontotemporal dementia is an umbrella term encompassing a group of **clinical syndromes** that are characterised by progressive changes in **behaviour**, **executive function**, or **language**. These syndromes include the behavioural variant of frontotemporal dementia and the non-fluent and semantic variants of primary progressive aphasia, each of which can also be accompanied by **amyotrophic lateral sclerosis**.

Frontotemporal lobar degeneration is the overarching **pathological term** for a **group of neurodegenerative disorders** that involve one or more **proteinopathies** and are typically associated with progressive degeneration, particularly in the **frontotemporal neural networks**.

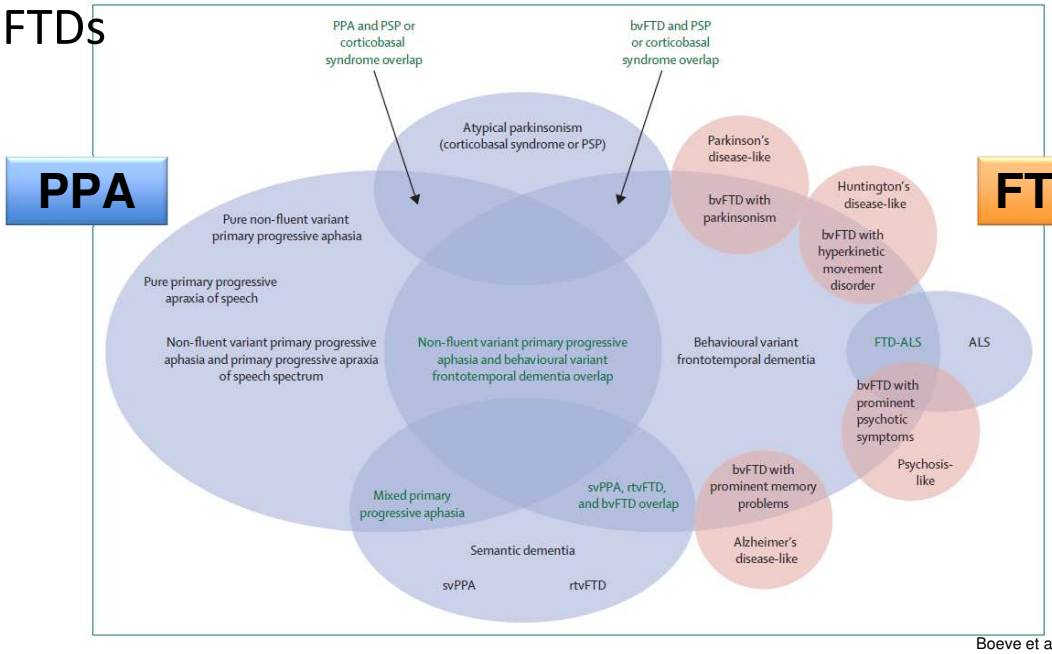
The major groups of proteinopathies include the **tauopathies** (eg, Pick's disease, progressive supranuclear palsy, and corticobasal degeneration), the **TDP43 proteinopathies**, and the **FET-related proteins**.

Lancet Neurol 2022; 21: 258–72

FTDs

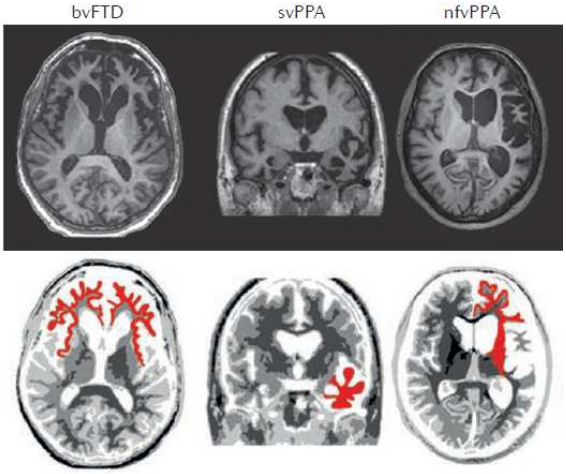
- Behavioral variant
  - Disinhibition, apathy, altered eating behavior, stereotypes, egocentrism
- Primary Progressive Aphasia
  - **Semantic v.**: fluency N, anomia, poorly informative…
  - **Non-fluent v.**: decreased fluency, agrammatism, speech apraxia
  - *Logopenic v.:* decreased fluency *with word-finding difficulty (AD>FTD)*
- Visuo-spatial disorders
  - Right temporal v.
- Variable severity of memory and dysexecutive impairments

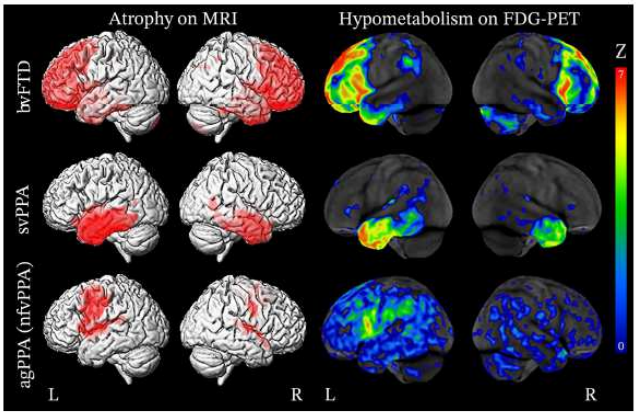
FTDs



Boeve et al. *Lancet Neurol 2022*

FTDs: Brain Atrophy & Hypometabolism



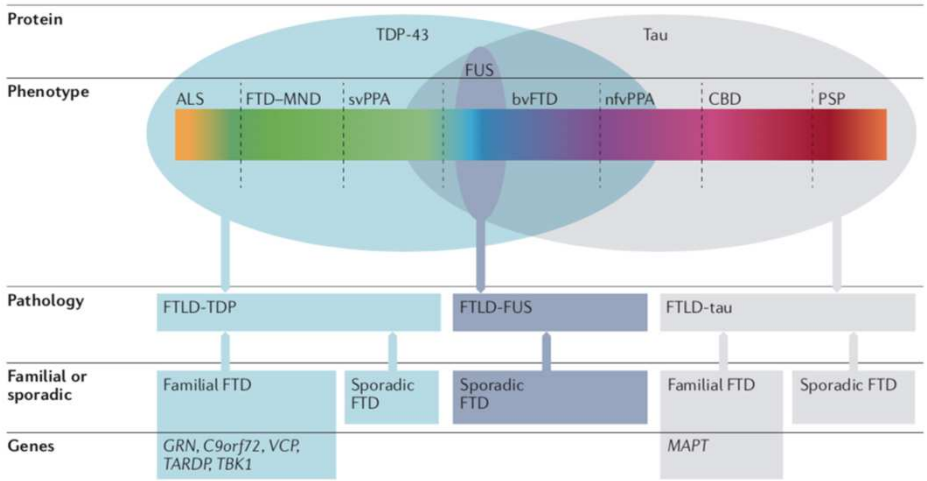


MEETER et al. *Nat Neurol Rev 2017*

Peet et al. *Neurotherapeutics 202*

FTLDs

Sporadic: 60-70%
Family Hx: 30-40%
AD in 15%



Meeter et al. *Nat Neurol Rev 2017*

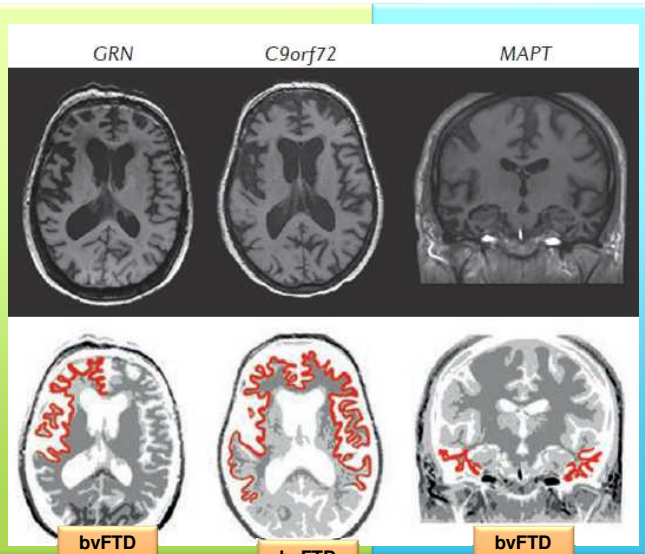
FTLDs: Brain Atrophy

Protein
TDP-43

FTLD-TDP
5 subtypes…

bvFTD
nfvFTD
svFTD

ALS



bvFTD
nfFTD

bvFTD

bvFTD
svFTD

Protein
Tau
MAPT (Chr 17)

Pick's
bvFTD
svFTD
nfvFTD

PSP
CBD

aFTLD-FUS
(<40yo)

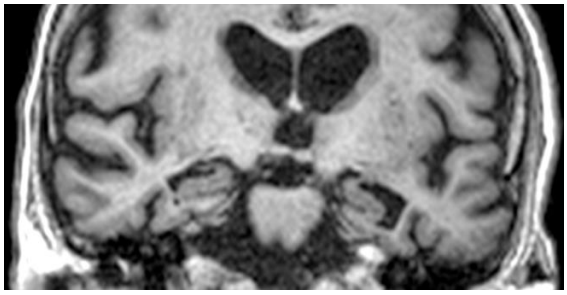
MEETER et al. *Nat Neurol Rev 2017*

A. KRAINIK, Grenoble - France

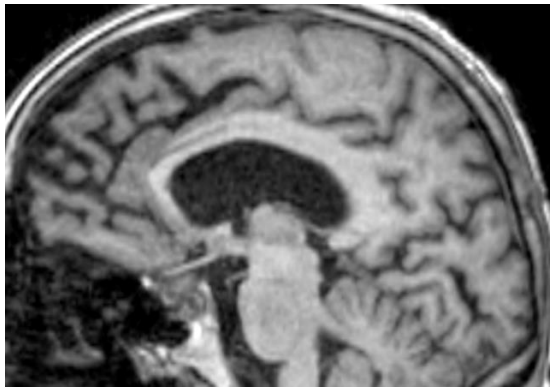
bvFTD

- W73yo, behavioural change (apathy, eating), dysexecutive and memory imp

Moderate Temporal + HC atrophy
L>R



GFPA Frontal +++

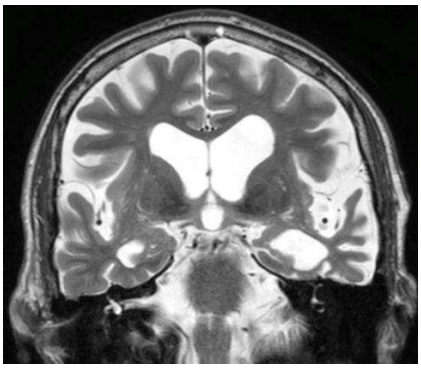


A. KRAINIK, Grenoble - France

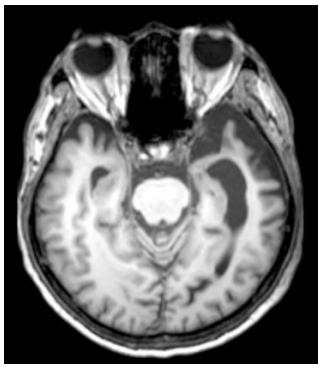
svPPA

- M75yo, Memory imp., PPA (↘ naming & semantic knowledge,…)

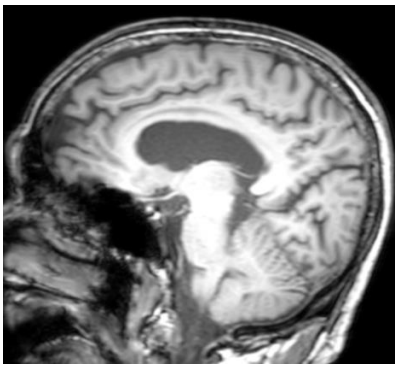
Severe Temporal + HC atrophy L>R



Extreme anterior temporal atrophy



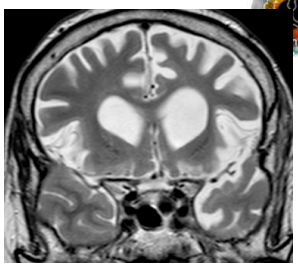
GFPA Ø



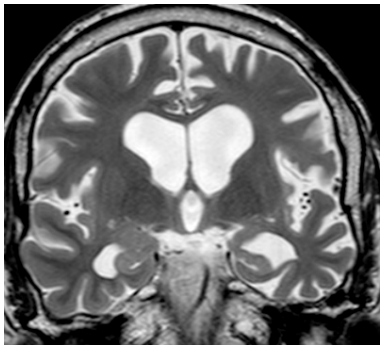
A. KRAINIK, Grenoble - France

nfvPPA

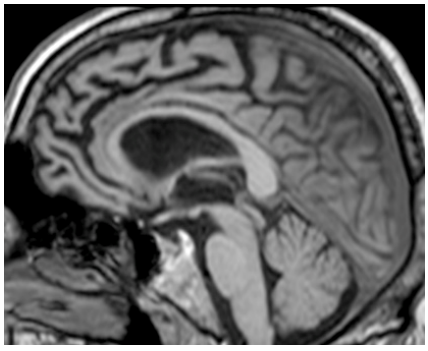
- M54a, PPA: ↘ fluency, grammatic error, BF apraxia

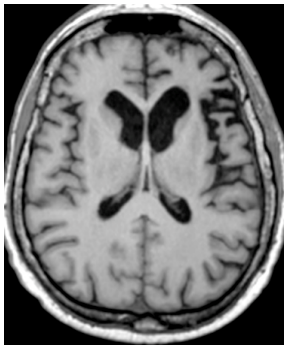


Temporal & HC atrophy L>R



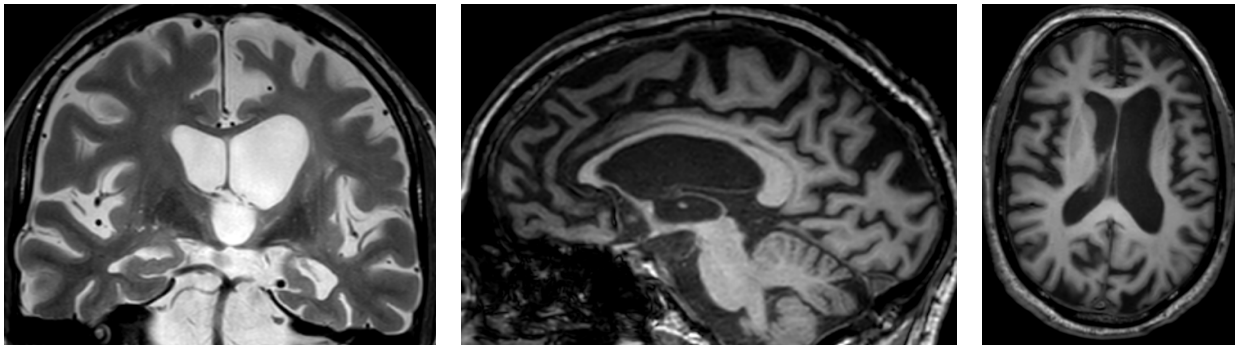
GFPA frontal



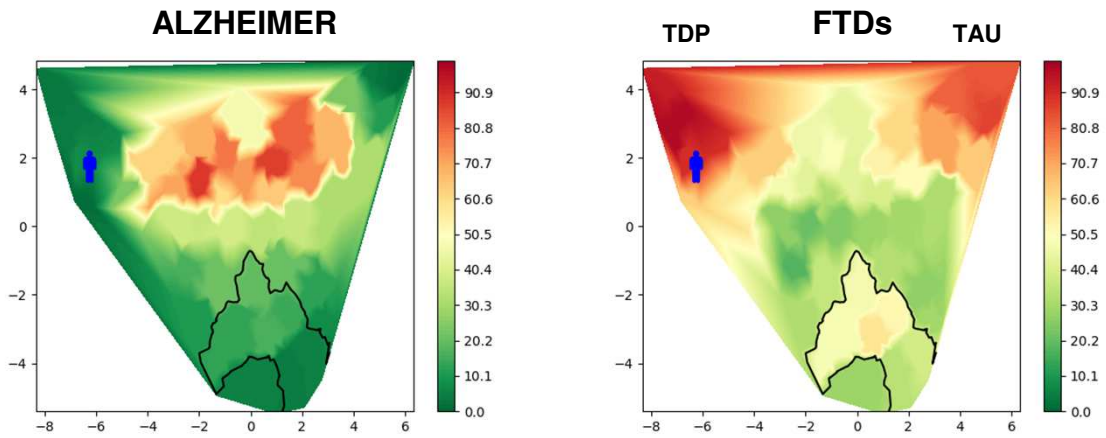


A. KRAINIK, Grenoble - France

M79yo, Speech & memory imp.



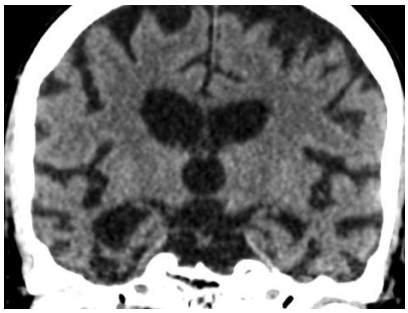
Dementia® GeodAIsics



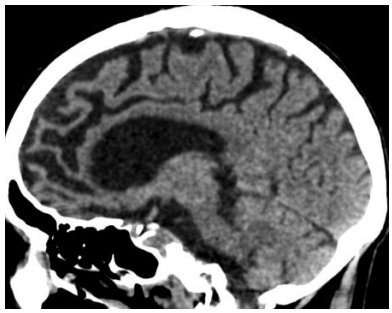
bvFTD

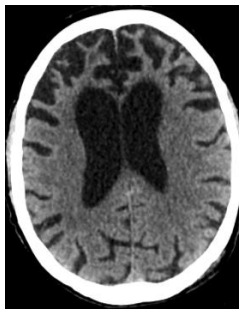
- M84yo, behavioural change (agressivity), dysexecutive and memory imp. MRI impossible

Severe Temporal + HC atrophy R>L



GFPA Frontal +++



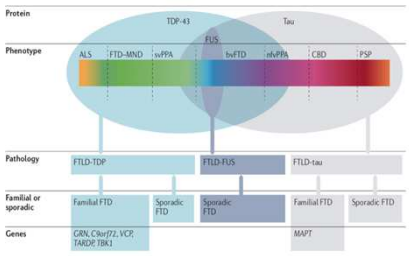


W55yo, rapidly progressive lPPA

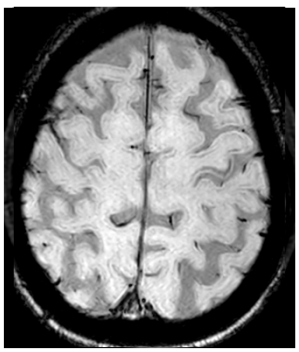
72111977

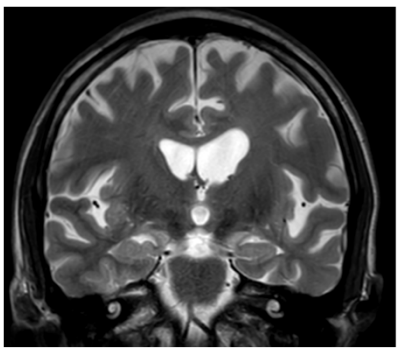
Right forearm myoclonia

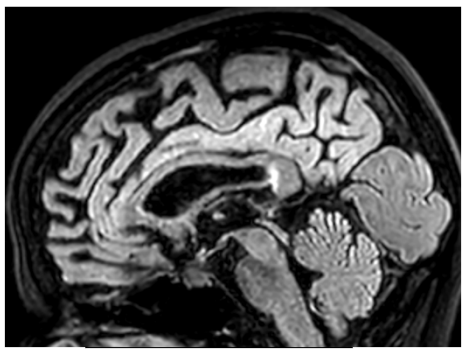
FTD + ALS



Meeter et al. *Nat Neurol Rev 2017*

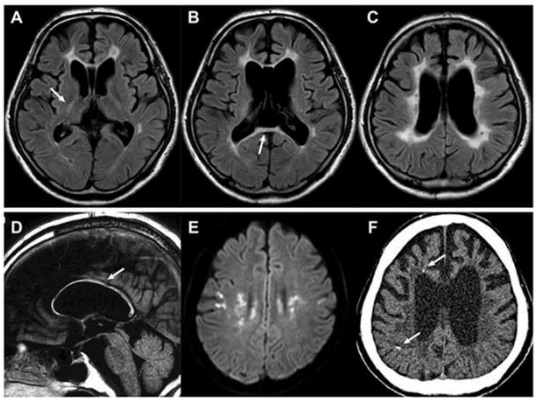






FTDs: no signal abnormalities ?

- MRI
  - HST2 WM (>80%)
    - Symetrical (63%)
    - Confluent (63%)
    - Frontal>Parietal>Temporal
    - U fibers (50%)
    - Corpus callosum (80%)
    - CST (63%)
  - Atrophy (95%)
    - Frontal > Parietal
    - Corpus callosum (90%)
  - BG, posterior fossa: very rare
  - Ca++: possible (punctuate, linear)
  - Contrast uptake: rare but possible
  - Spinal cord: HST2 CST



Konno Eur J Neurol 2018

Adult-onset Leukoencephalopathy with axonal Spheroids and Pigmented glia (ALSP): Chr 5 CSF1R gene mutation

THM 3: MRI in FTDs

- FTDs nosology is WIP
- Clinical data are mandarory
- Imaging may support clinical and biological abnormalities, helpful for DDx
- MRI better illustrates lobar atrophy
- Segmentation & classifier softwares may help

MR Imaging in DLB

Dementia with LEWY BODIES

Overview

- DLB: 10-15% dementia (AD: >50%)
- Neurodegenerative disease in elderly (αsyn. ± βAmyl)
- Lewy bodies: brain stem, BG, l. limbic, occipital…
- Cholinergic dysfonct ➔ ACE inhibitor

4th consensus report of DLB consortium

- Fluctuating cognitive disorders: Attention, alertness
- Recurrent visual hallucinations
- Spontaneous parkinsonism (poss delayed): L-Dopa -
- REM sleep disorder
- Adverse reactions to neuroleptic
- CSF: non AD profile

McKeith et al. 4th consensus report of DLB consortium *Neurology 2017*

Table 3. Revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB) (2017)

- **Central feature**: *Essential for a diagnosis of DLB*
  Dementia. In the early stages, prominent memory impairment may not occur, but deficits of attention, executive function, and visuoperceptual ability may be prominent.
- **Core clinical features** (The first 3 typically occur early and may persist throughout the course)
  - Fluctuating cognition with pronounced variations in attention and alertness
  - Recurrent visual hallucinations that are typically well formed and detailed
  - Rapid eye movement (REM) sleep behavior disorder (RBD), which may precede cognitive decline
  - One or more spontaneous cardinal features of parkinsonism: bradykinesia, resting tremor, or rigidity
- **Supportive clinical features**
  Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, or urinary incontinence); hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; and apathy, anxiety, and depression
- **Indicative biomarkers**
  - Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT/PET
  - Abnormal (low uptake) ^{123}I-MIBG myocardial scintigraphy
  - Polysomnographic confirmation of REM sleep without atonia
- **Supportive biomarkers**
  A relative preservation of medial temporal lobe structures on CT/MRI scan; generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging; prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

should be used, and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

McKeith et al. 4th consensus report of DLB consortium *Neurology 2017*

Yamada *J Mov Dis 2020*

Indicative biomarkers

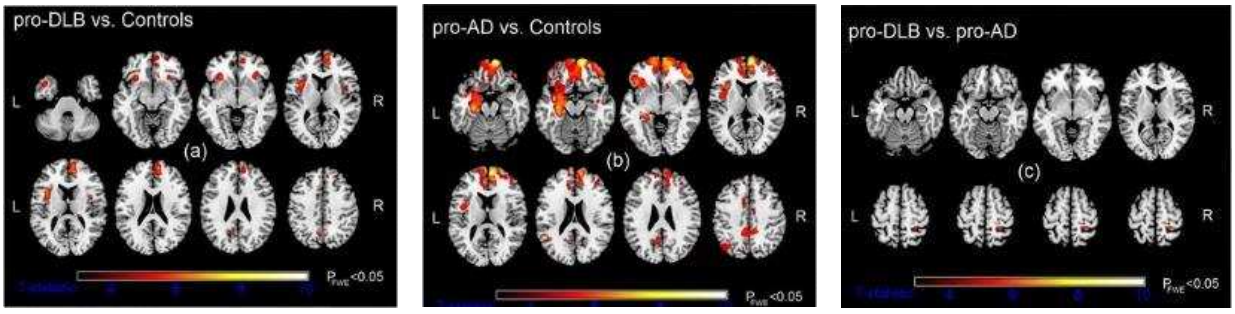
- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT/PET
- Abnormal (low uptake) ^{123}I-MIBG myocardial scintigraphy
- Polysomnographic confirmation of REM sleep without atonia

Supportive biomarkers

A relative preservation of medial temporal lobe structures on CT/MRI scan; generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging; prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

Brain volume changes

DLB (28 pro): insular atrophy…



Blanc *Alzheimers Res Ther 2016*

Brain volume changes

- Insular atrophy…
- No significant atrophy in
  - Temporal lobe
  - Hippocampus
  - Parieto-occipital lobes (except for hallucinators…)
- Poorly helpful
- Discrepancy between severity of cognitive disorders and mild atrophy +++

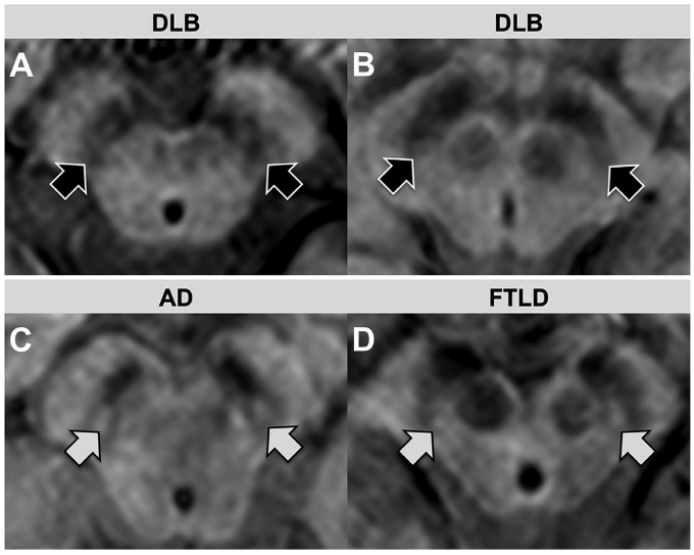
Nigrosomes 1

Nigrosome loss in DLB

- Se 63%, Sp 79%
- PPV 44%, NPV 89%...
  Shams AJNR 2017

- Se 80% Sp 76% Rizzo J Alz Dis 2019

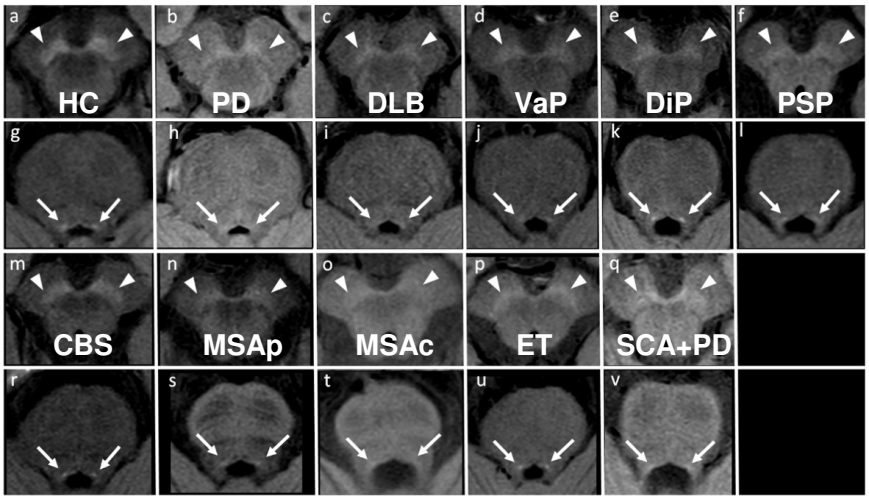
Se 62% vs 92% in PD
personal experience E. Sayilir MD Thesis ECR 2024



Haller *Radiology 2021*

Neuromelanin loss

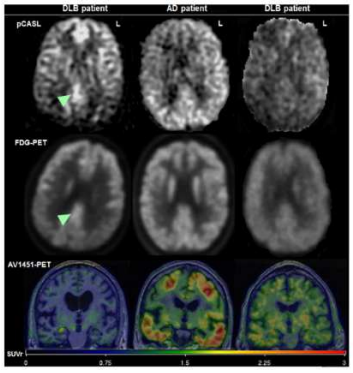
- HST1 in SN, LC
- ↘ NM in PD, DLB, PSP, MSA
- Normal NM in VaP, DiP, CBS, ET



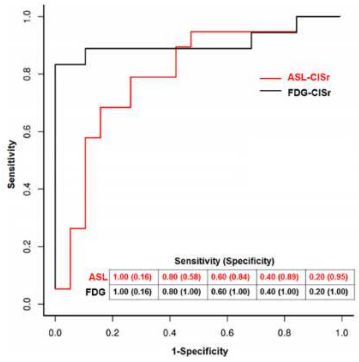
Matsura *Park Rel Dis 2021*

Perfusion & Metabolism

Posterior impairment with cingular island



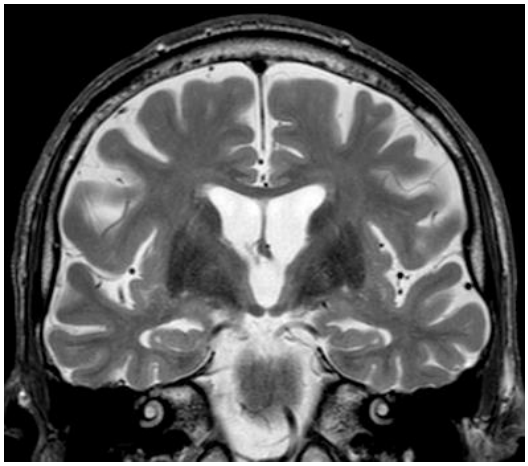
AUROC PET/ASL = 0.91/0.80

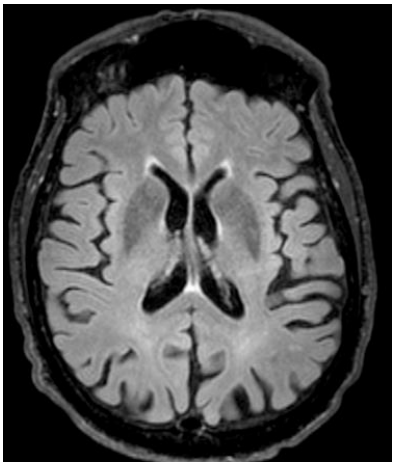


Nedelska *Neuroimage Clinical 2018*

M77y. Cognitive decline (memory, dysexecutive sd, behaviour). Sleep dis, visual hallucinations. Mild EP sd, no L-DOPA sensitivity

652605

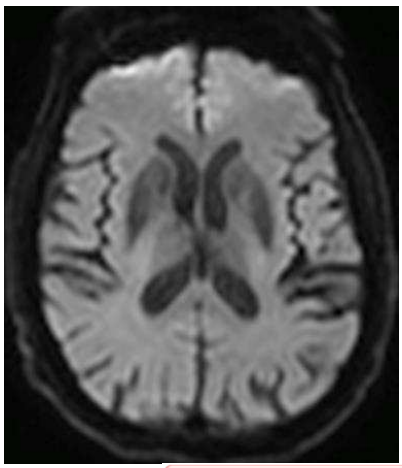


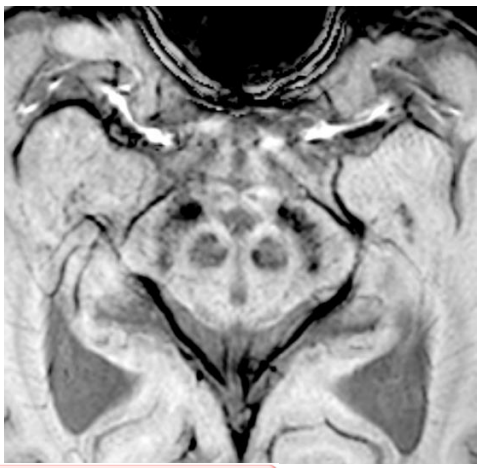


A. KRAINIK, Grenoble - France

M77y. Cognitive decline (memory, dysexecutive sd, behaviour). Sleep dis, visual hallucinations. Mild EP sd, no L-DOPA sensitivity

652605



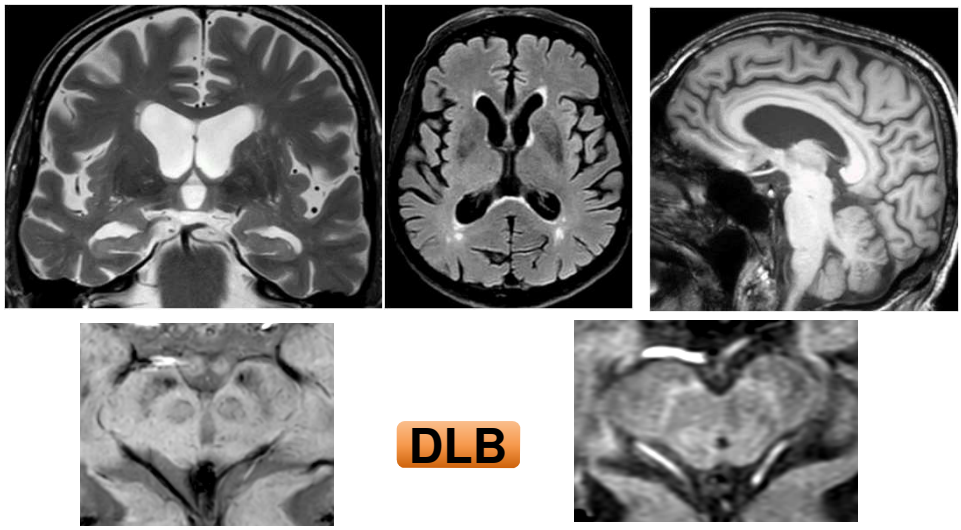


DLB

A. KRAINIK, Grenoble - France

M85. Fluctuating cognitive decline (memory, dysexecutive sd, behaviour). Visual hallucinations. No EP sd.

747106

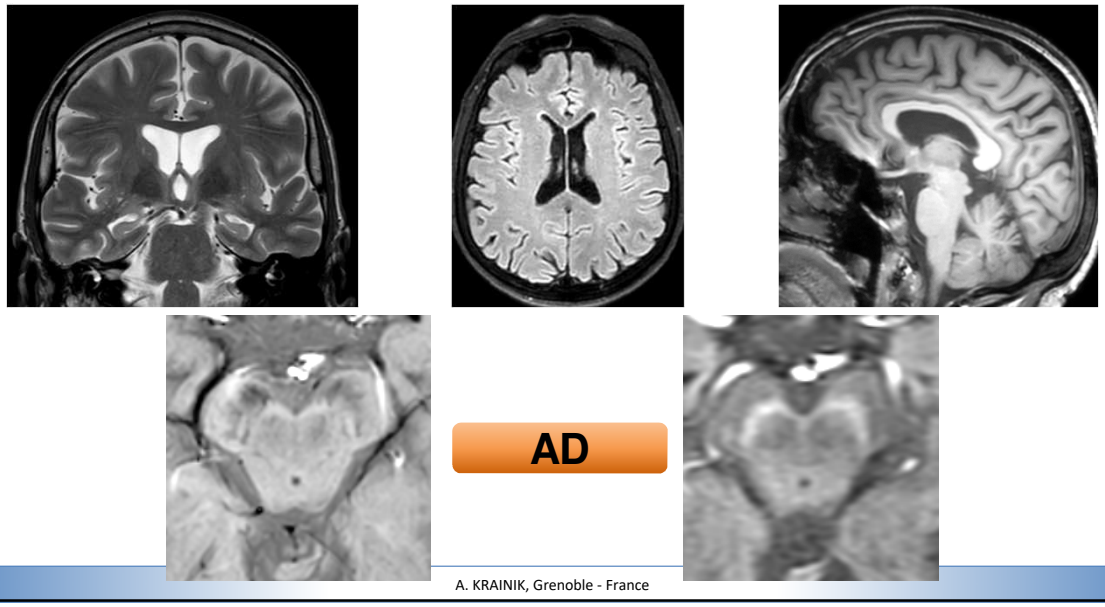


DLB

A. KRAINIK, Grenoble - France

F67, Memory decline and sleep disorders

226055

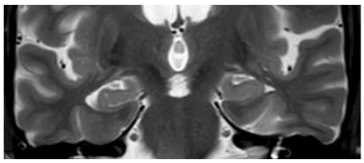


AD

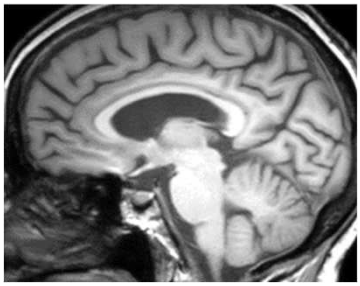
A. KRAINIK, Grenoble - France

W70y, cognitive dis. dysexecutive sd > memory impairment.
No sleep dis, no visual hallucinations
No extraP sd. CSF normal

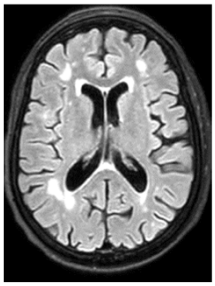
Mild hippocampal atrophy



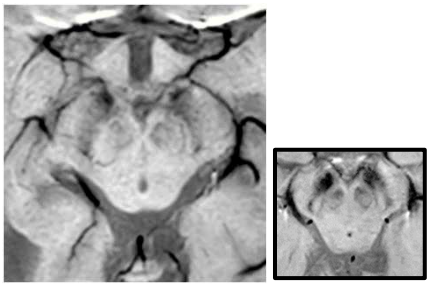
GFPA Ø



Moderate T2 WMH



SWI: Loss of nigrosome 1



A. KRAINIK, Grenoble - France

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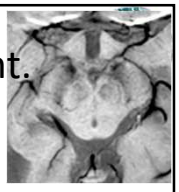
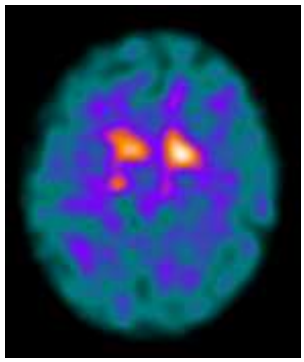
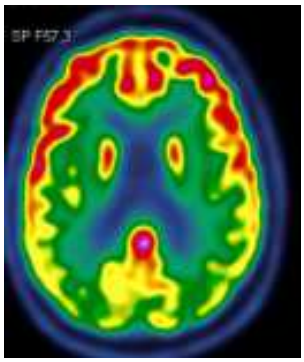


Cerebral SPECT DATScan



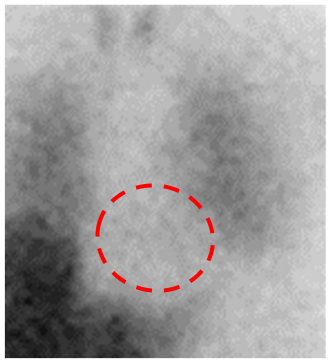
Presynaptic dopaminergic loss
Lower uptake in posterior putamen

Cerebral PET FDG



Posterior hypometabolism

Myocardial SPECT MIBG



No myocardial uptake
Sympathetic dysfonction (PD,...)

DLB

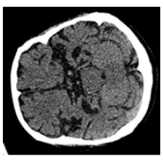
THM4: MRI in DLB

- Clinical data+++ Meet the clinician and the patient !
- MR for DDx (& D+…)
  - **SWI: nigrosome loss**
  - **NM: SN/LC loss**
  - **3DASL: posterior hypoperfusion**
- NM: DaTSCAN, PET FDG, Myocardial MIBG SPECT, … α-synuclein, τ, amyloid

MR Protocol

- **Atrophy**: 3DT1 GRE IR
  - Temporo-hippocampal (Scheltens)
  - Parietal
  - Fronto-parietal gradient (Sag + Ax)
  - Segmentation softwares (age)
- **GM, SN**: SWI, DWI (NM, ASL)
  - Cortex, BG, Nigrosomes
- **Vascular lesions**: 3DFLAIR, SWI, DWI
  - HST2 GM, WM (Fazekas), CMBs, CSS…

- MRI IV-
  - 3D T1 GRE IR
  - Coro hippo : MPR / 2D T2 / 2D T1IR
  - 3D FLAIR
  - SWI / T2*
  - DWI
  - **Opt**: neuromelanine, ASL, **GD**
- Otherw. Plain CT
  - When impossible MRI
  - MPR coro, sag



To remember

- **Dementia is a clinical diagnosis**; imaging supports **etiology**
- **Alzheimer's disease is the most common cause**; main alternatives: **FTLD, DLB**
- **Clinical ± biological data are mandatory** and must guide interpretation and communication
- **Non-contrast CT (± MPR)** excludes **surgically treatable causes** when MRI is not feasible
- **MRI is the reference modality:** *3D T1 · 3D FLAIR · DWI · SWI*
- **Advanced MRI** refines DDx: *Neuromelanin, ASL perfusion (esp. DLB); vascular involvement*
- **New AD therapies make MRI pivotal** to **address diagnostic and therapeutic challenges:** *patient selection, risk assessment, monitoring*

THANK YOU FOR YOUR ATTENTION

NEURORADIOLOGY
GRENOBLE
FRANCE

AKRAINIK.EDU@GMAIL.COM