Distinguere la demenza di Alzheimer dalla demenza a corpi di Lewy

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What's on in DLB?

- ✓ Challange 1: sensitivity of diagnostic criteria
- ✓ Challange 2: diagnostic specificity and pathological comoribidity
- ✓ Challange 3: Definition of prodromal DLB
- ✓ …and hence need of biomarkers

Not so rare

Lewy bodies pathology is common:

community dwelling older subjects: **18% of cases**

dementia patients: **15-20%**

Alzheimer's disease comorbidity in half cases

Prevalence (clinical diagnosis)

- Community setting: **4.2%**
- Secondary care setting: **7.5%**

Schneider et al, Brain 2012, Jellinger; 2011; Vann Jones, Psychol Med 2014

But…

RESEARCH Open Access

Clinical prevalence of Lewy body dementia

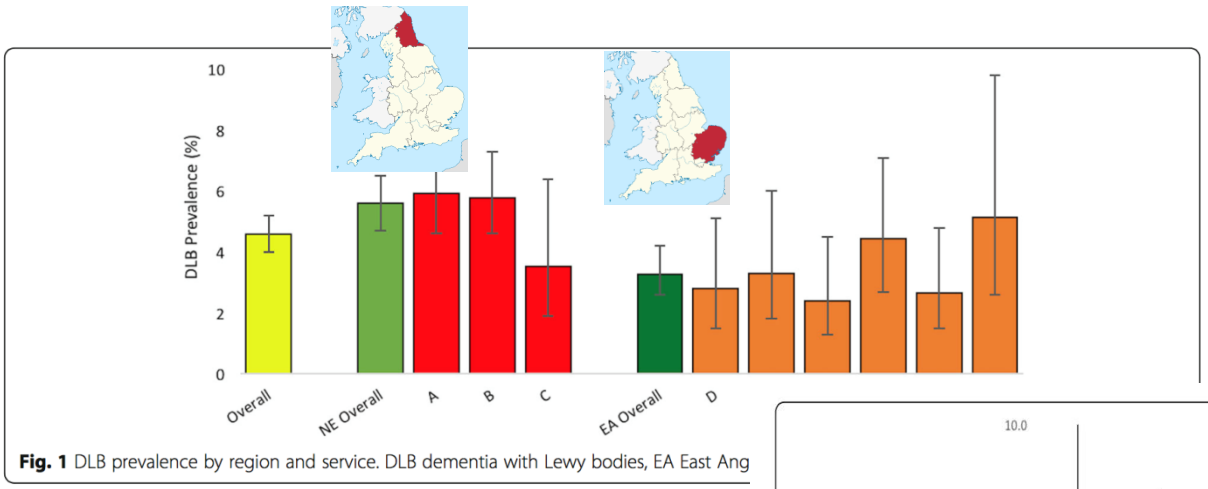


Fig. 1 DLB prevalence by region and service. DLB dementia with Lewy bodies, EA East Ang

4.6% of all diagnoses (ranging 2.5-6%)

More frequently diagnosed in young subjects

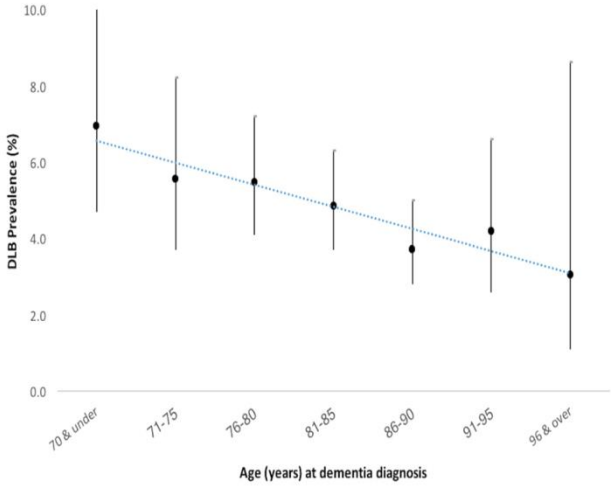


Fig. 2 DLB prevalence and age at dementia diagnosis. DLB dementia with Lewy bodies

O' Brien 2018

Why revised diagnostic criteria?

Low sensitivity in clinical setting (Nelson, 2014)

Atypical DLB is now recognized

Some core features may never be present
(25% no motor signs)

More weight on “indicative” biomarkers

VIEWS & REVIEWS

Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

OPEN

Essential
Dementia (visual-spatial/attention)

Core clinical features			
Fluctuations	Visual Hallucinations	RBD	Parkinsonism

Indicative Biomarkers
↓ DA uptake in the basal ganglia (SPECT o PET)
Polysomnography (confirmed REM without atonia)
↓ Uptake ^{123}I-MIBG (cardiac scintigraphy)

- **PROBABLE DLB=**
  - 2 core features
  - 1 core feature + 1 indicative biomarker
- **POSSIBLE DLB=**
  - 1 core feature
  - 1 indicative biomarker

McKeith 2017

3 minutes to make diagnosis of DLB

Lewy body composite risk score (≥3)

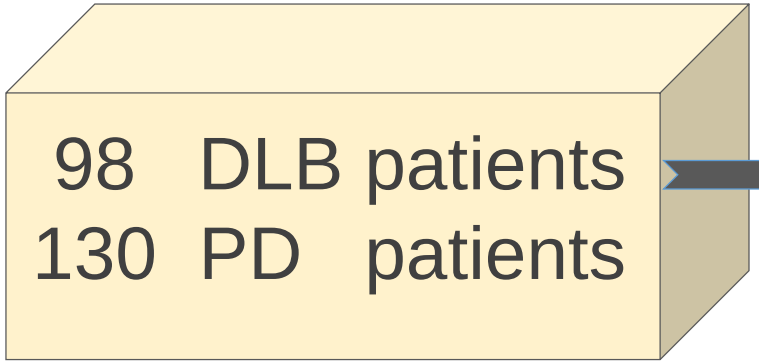
motor

Sleep/wake, fluctuation, RBD, VH

Please rate the following physical findings being present or absent for the past 6 months and symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient...	Yes	No
Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?		
Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?		
Have a loss of postural stability (balance) with or without frequent falls?		
Have a tremor at rest in any of the 4 extremities or head?		
Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		
Have episodes of illogical thinking or incoherent, random thoughts?		
Have frequent staring spells or periods of blank looks?		
Have visual hallucinations (see things not really there)?		
Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?		
Have orthostatic hypotension or other signs of autonomic insufficiency?		
Total		

Galvin, Alz&Dementia 2015

EXTRAPYRAMIDAL SIGNS IN DLB



68 % EPS +

- Body bradykinesia
- Action tremor
- Facial expression
- Gait instability

DLD>PD

MIXED TREMOR

PIGD

- Rest tremor
- Rigidity

DLB<PD

Severity did not correlate with age, disease duration, cognition

AARSLAND, 2001

Sleep-wake/fluctuation cluster

RBD upgraded to core feature

Hypersomnolence

Transient episodes of unconsiousness

added among suggestive features

Polysomnography added as indicative biomarker

SLEEP-WAKE in DLB

Sleep

frequent RBD-like symptoms (70%)

Wake

increased somnolence

increased number of daytime naps

daytime dysfunction due to somnolence

fluctuation of attention (associated with RBD+)

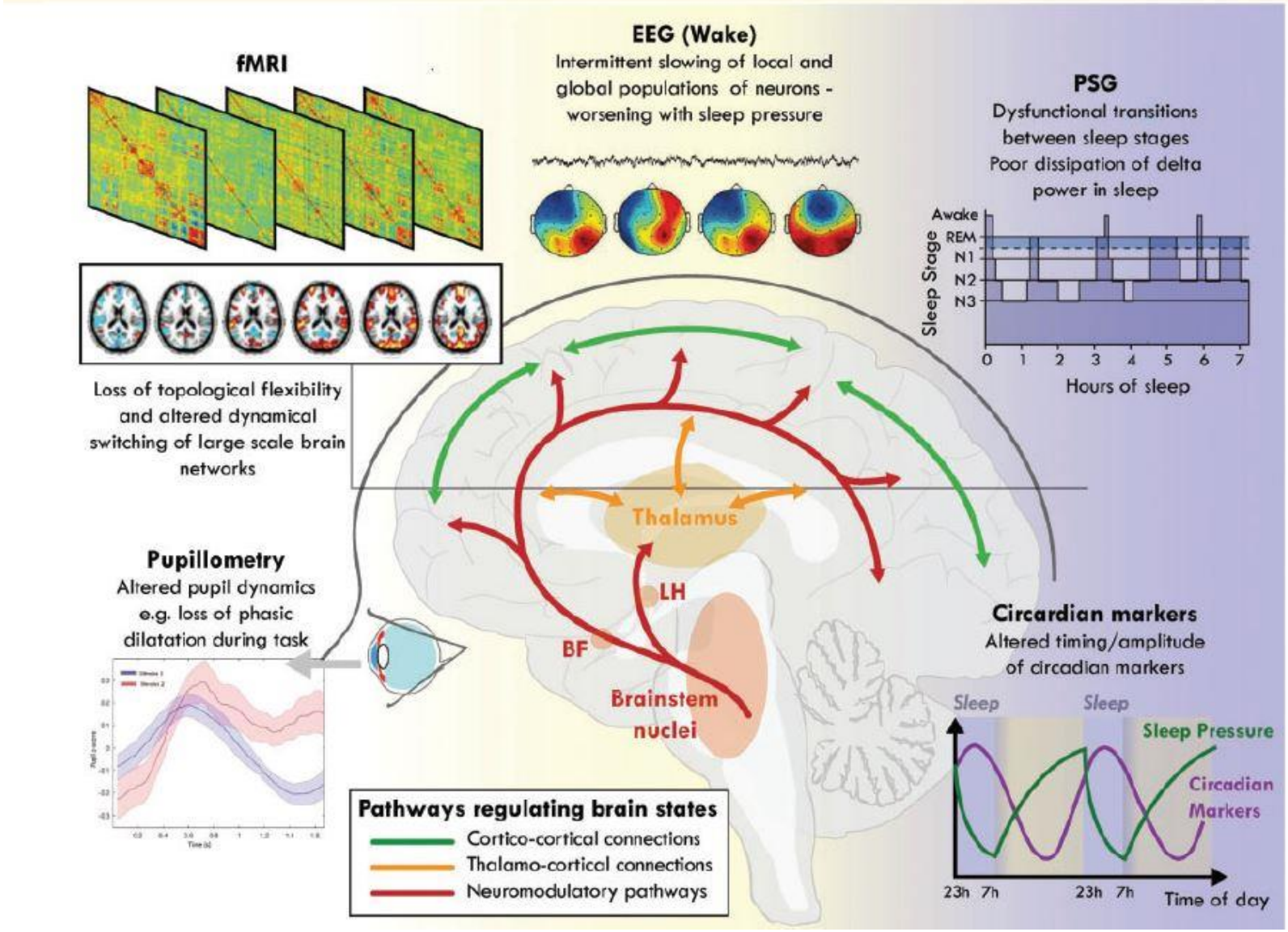
Cagnin et al, JAD 2017

FLUCTUATIONS

Spontaneous alterations in

- Cognition
- Attention
- Arousal

- *Behavioural inconsistency*
- *Disorganized speech*
- *Altered consciousness-lethargy*


fMRI
Loss of topological flexibility and altered dynamical switching of large scale brain networks
EEG (Wake)
Intermittent slowing of local and global populations of neurons - worsening with sleep pressure
PSG
Dysfunctional transitions between sleep stages
Poor dissipation of delta power in sleep
Awake
REM
N1
N2
N3
Sleep Stage
0 1 2 3 4 5 6 7
Hours of sleep
Thalamus
LH
BF
Brainstem nuclei
Pupillometry
Altered pupil dynamics e.g. loss of phasic dilatation during task
Circardian markers
Altered timing/amplitude of circadian markers
Sleep
Sleep
Sleep Pressure
Circadian Markers
23h 7h
23h 7h
Time of day
Pathways regulating brain states
Cortico-cortical connections
Thalamo-cortical connections
Neuromodulatory pathways

Brain 2019

EEG nella DLB

Analisi degli spettri:

- frequenza dominante: **pre- alfa / theta (5,6- 7,9 Hz)** prevalente nelle derivazioni **posteriori**
- fluttuazioni delta- theta/pre- alfa o theta- pre- alfa/alfa
- correlazioni con **fluttuazioni cognitive**

Studio delle sorgenti di attività elettrica cerebrale:

- attività **diminuite nelle derivazioni occipitali e sensori- motorie.**
- correlazioni con peggiori funzioni cognitive.

Studio di complessità: → **Nessuno studio a disposizione nella DLB**

Cromarty, R. A. *et al.,* 2016*, Clin. Neurophysiol.*; Bonanni, L. *et al*., 2008, *Brain* ; Stylianou, M. *et al.,* 2008, *Clin. Neurophysiol.* Bonanni, L. *et al.*, 2016, *Alzheimer's Dis.*; Babiloni, C. *et al.,* 2018, *Alzheimer's Dis.*; Aoki, Y. *et al.*, 2019, *Neuropsychobiology*

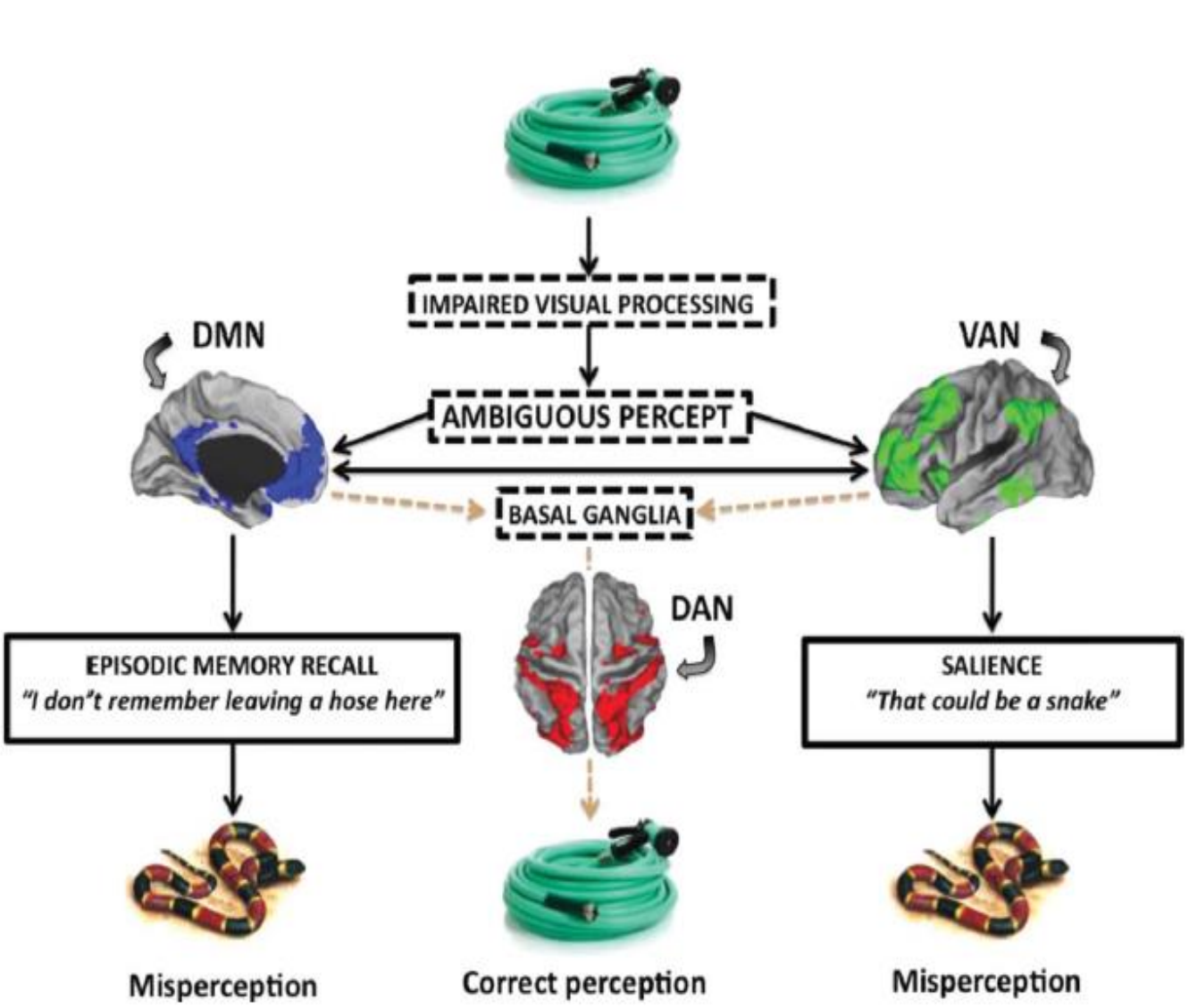
Open issues

- ✓ PSG *versus* RBD questionnaires?
- ✓ Diagnosis of RBD *versus* NON REM sleep behavioural disorder (i.e. confusional awakenings, …..)?
- ✓ ESS *versus* other scales dedicated to dementia
- ✓ Definition of outcomes for interventional treatments?

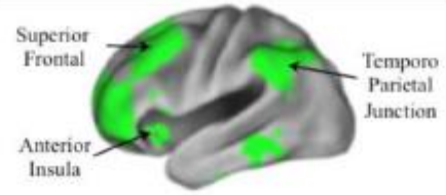
Anatomical correlates of VH

- Associated with poor visual attention
- Long fibers tracts dysconnection mainly in the righy hemisphere
- Imbalance between attentional functional networks

FUNCTIONAL CORRELATES OF VH

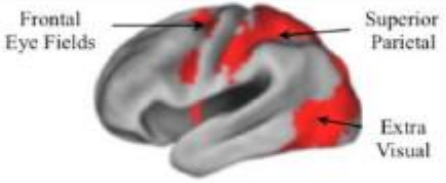


Ventral Attention Network



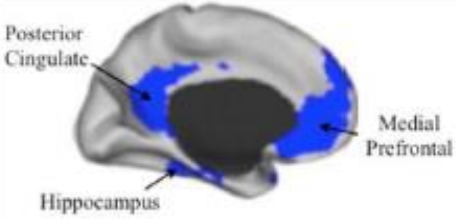
Mediate activation of other networks
Engages attention to salient stimuli

Dorsal Attention Network



Voluntary orienting
Cognitive information processing

Default Mode Network

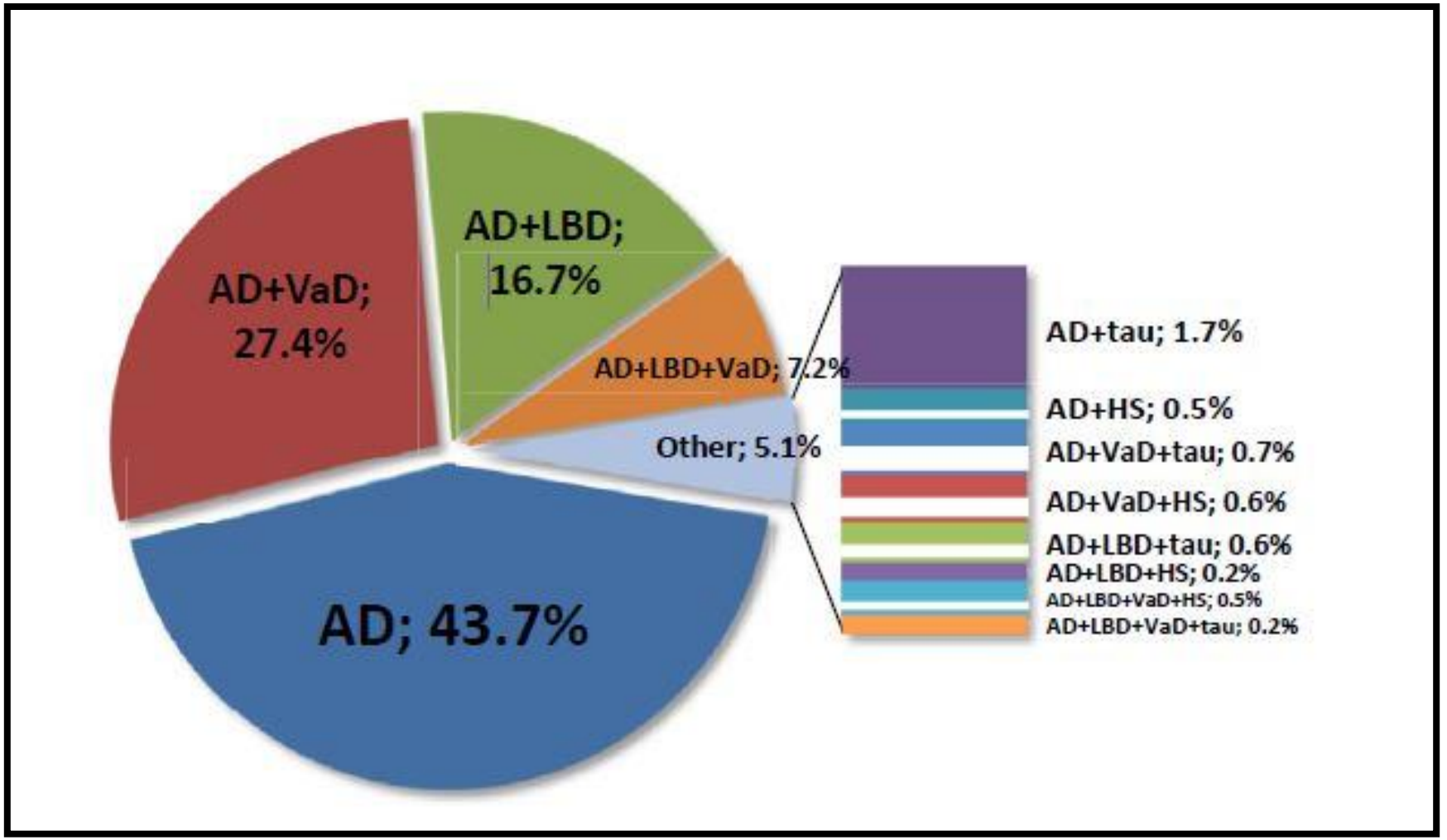


Task-independent thought
Mind wandering

What's on in DLB?

- ✓ Challange 1: sensitivity of diagnostic criteria
- ✓ **Challange 2: diagnostic specificity and pathological comorbidity**
- ✓ Challange 3: Definition of prodromal DLB
- ✓ …and hence need of biomarkers

Brain comorbidity in real life



Rabinovici, 2017

Person-specific contribution of neuropathologies to cognitive loss in old age

Patricia A. Boyle[1,2], **Lei Yu**[1,3], **Robert S. Wilson**[1,2,3], **Sue E. Leurgans**[1,3], **Julie A. Schneider**[1,3,4], and **David A. Bennett**[1,3]

- ✓ Comorbidity is the rule : 3/4 has 2 or more co-pathologies
- ✓ 230 combinations
- ✓ AD is the most virulent accounting for an average of 50% cognitive loss but individual contribution is variable

Ann Neurol, 2018

Heterogeneity of presentations

- Additional pathology
- Age
- Genetic variability of a-synuclein
- Different route of entry

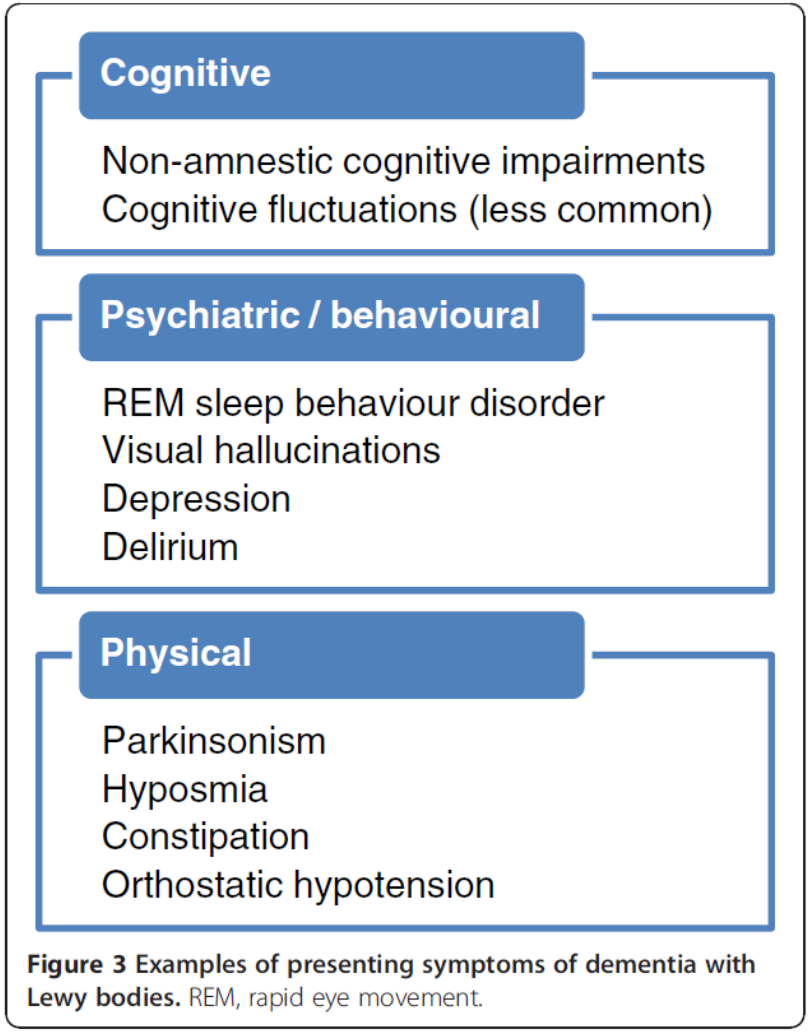


Figure 3 Examples of presenting symptoms of dementia with Lewy bodies. REM, rapid eye movement.

Additional pathology

66% of DLB brains will have AD pathology

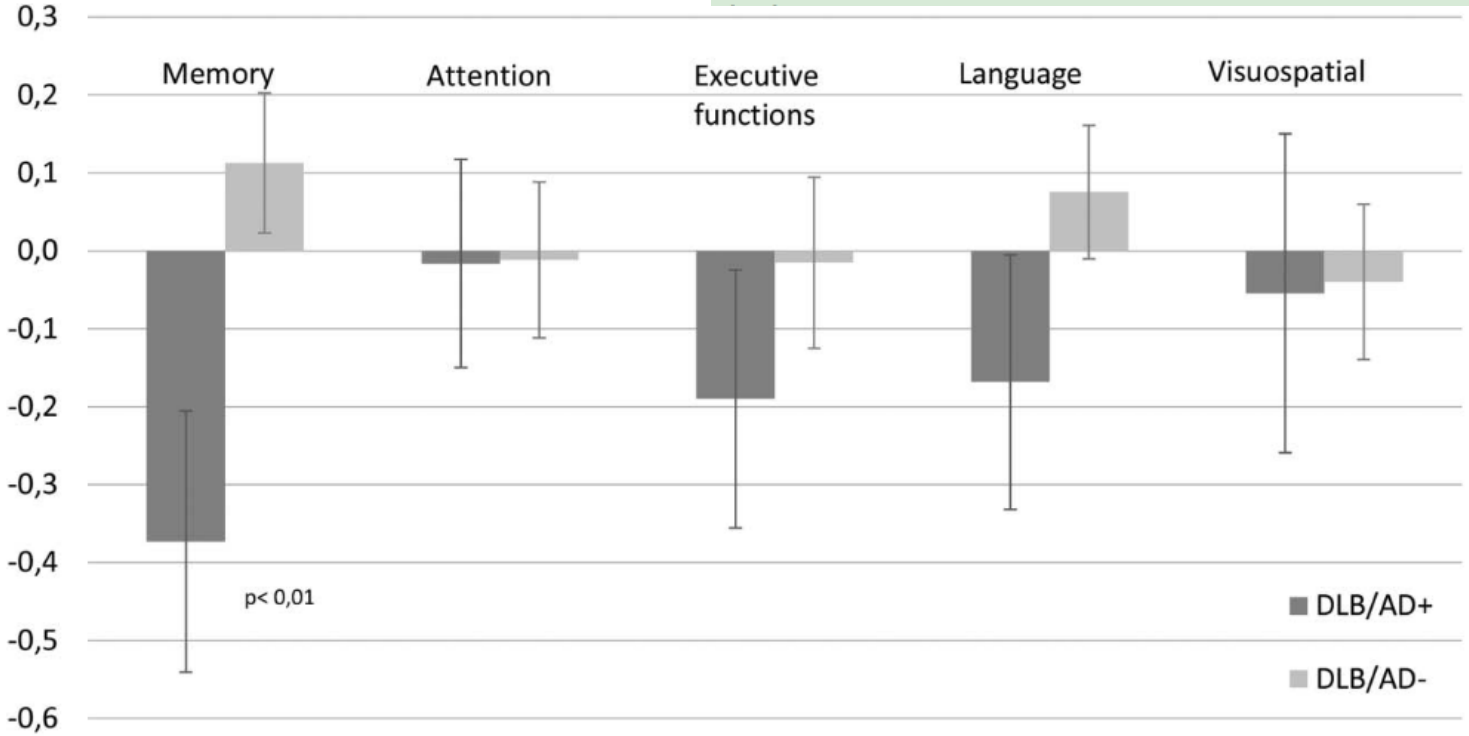
DLB phenotype is driven by alpha synuclein and neuritic plaques

AD pathology has an additive effect on clinical variables

RESEARCH PAPER

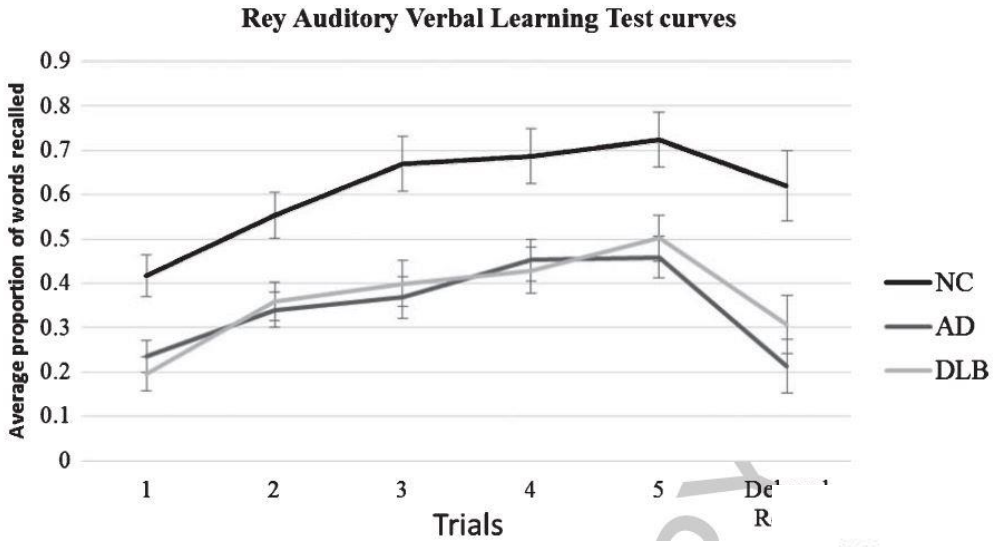
Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies

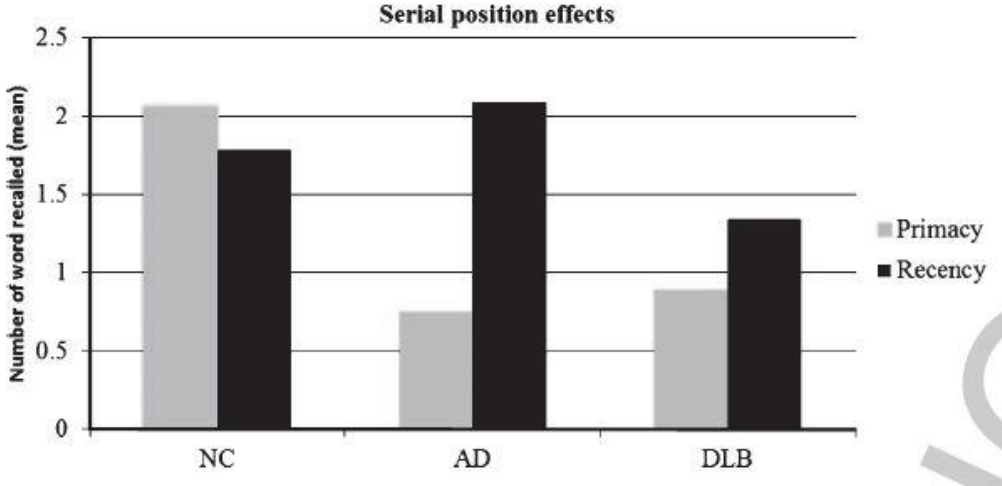
	DLB/AD+	DLB/AD-	
NPI[d]			
Total score	12.0 (6.5–21.5)	10 (5.0–16.0)	0.421
Delusions	7/31(23%)	4/59 (7%)	**0.043**
Hallucinations	17/31 (55%)	17/59 (29%)	**0.016**



Lemstra, JNNP 2016

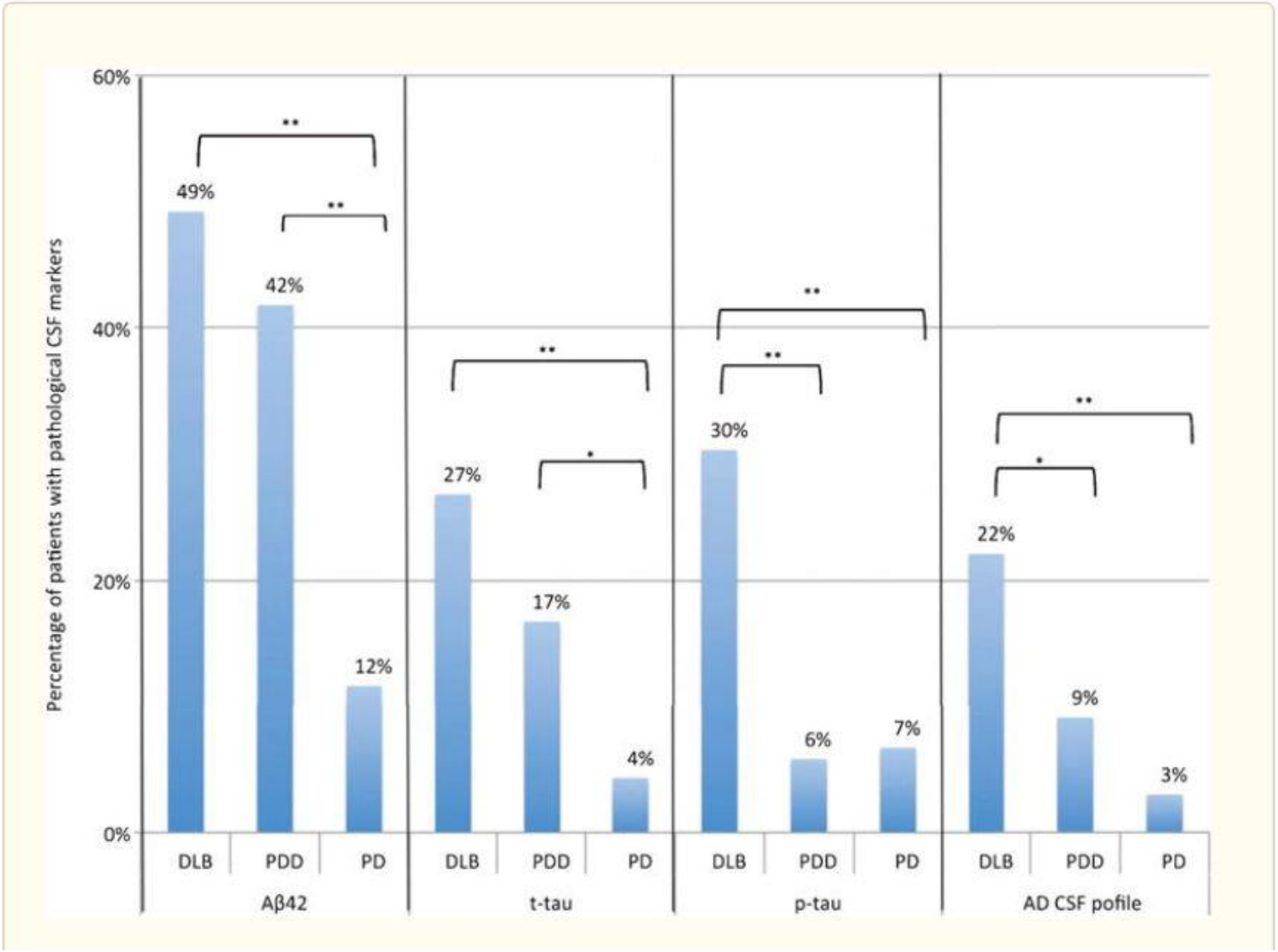
Specific Verbal Memory Measures May Distinguish Alzheimer's Disease from Dementia with Lewy Bodies



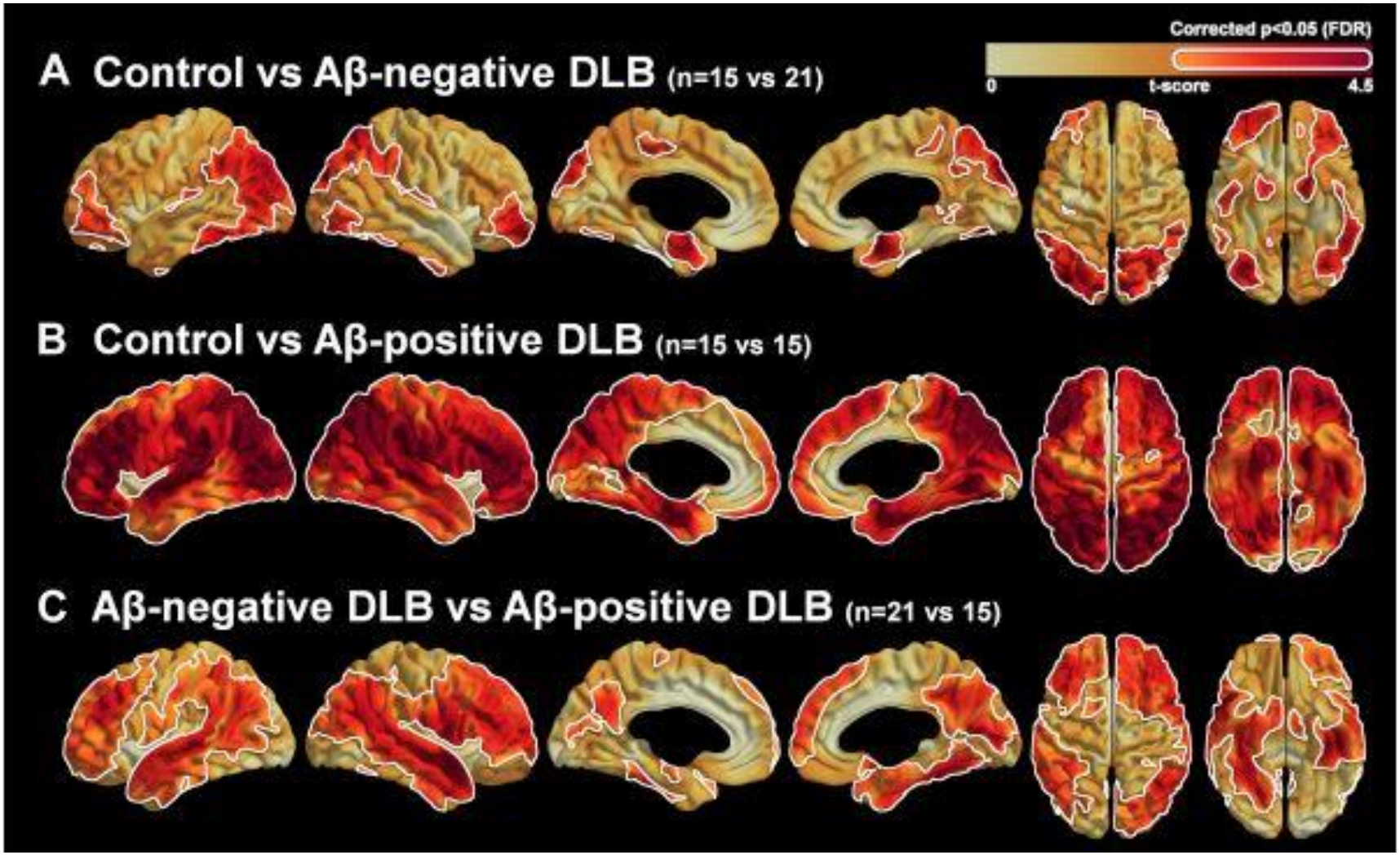


Bussè et al, JAD 2018

AD-like CSF biomarkers



Cortical thinning



Seok, Neurobiol Aging 2018

RESEARCH PAPER

Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies

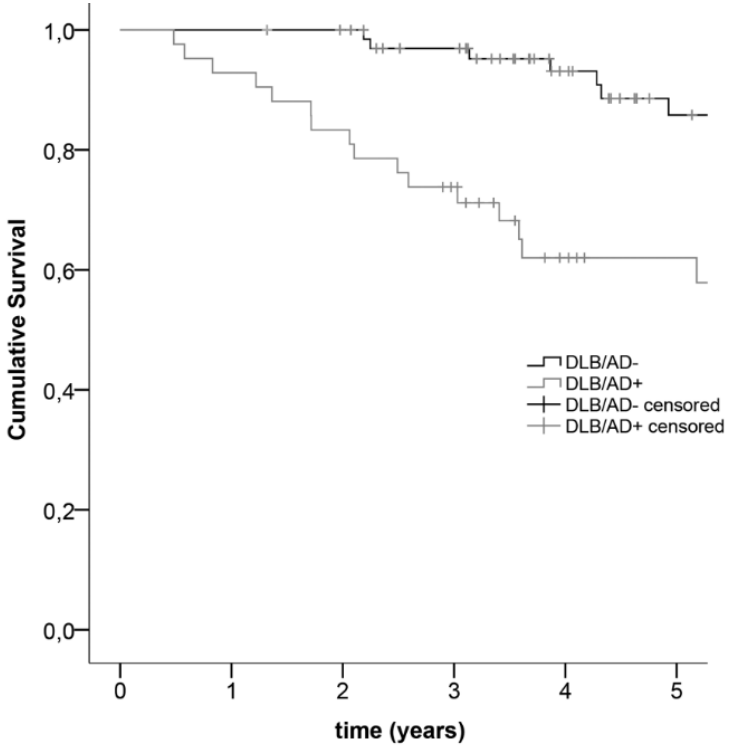


Figure 3 Effect of the dementia with Lewy bodies (DLB)/Alzheimer's disease (AD) positive cerebrospinal fluid (CSF) biomarker profile on admittance to nursing home. Kaplan-Meier curve of admittance to nursing home of DLB patients with the AD CSF profile and DLB/AD– CSF profile

or

What's on in DLB?

- ✓ Challange 1: sensitivity of diagnostic criteria
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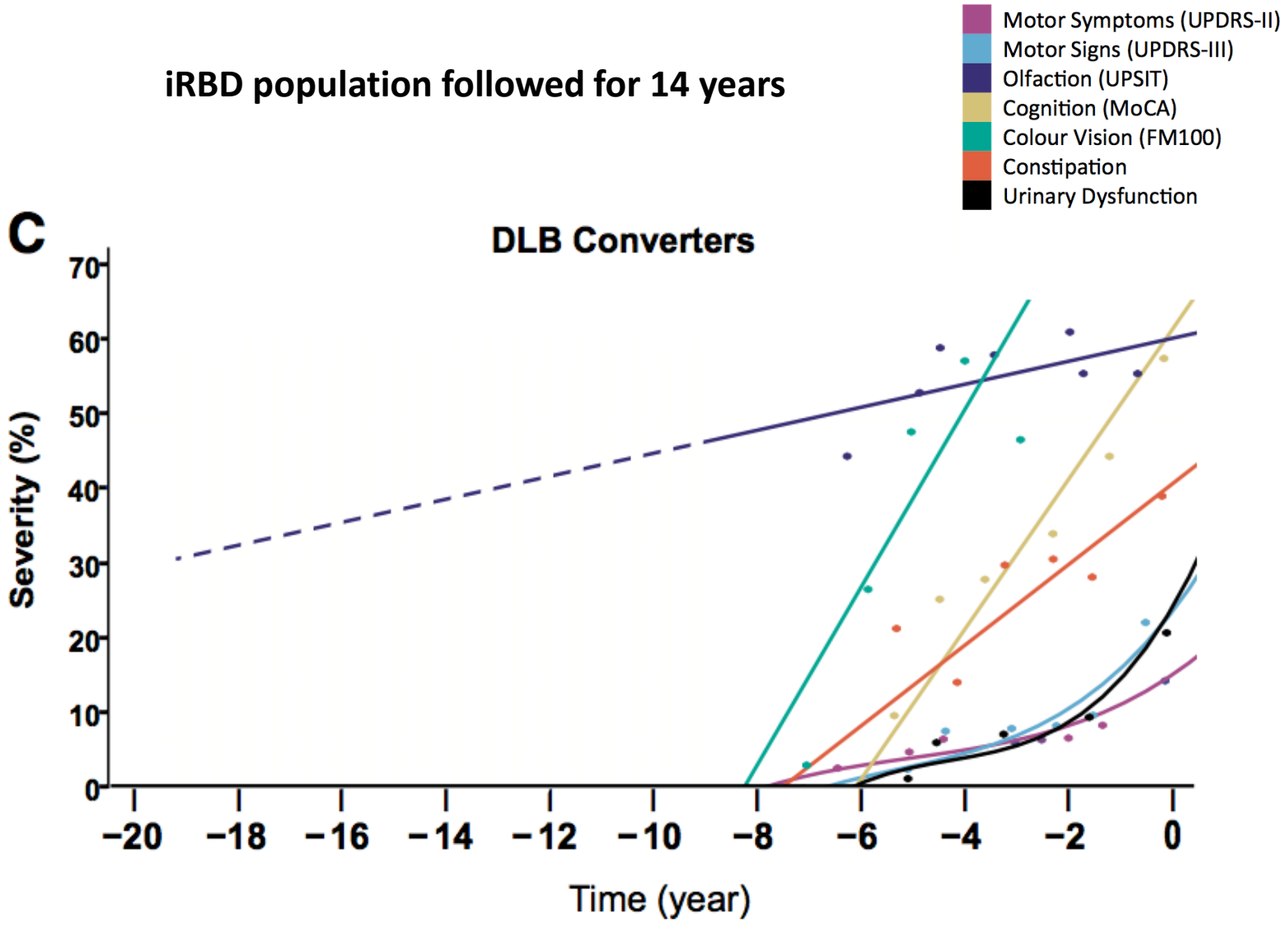
- ✓ **Challange 3: Definition of prodromal DLB**
- ✓ …and hence need of biomarkers

Prodromal DLB

iRBD population followed for 14 years

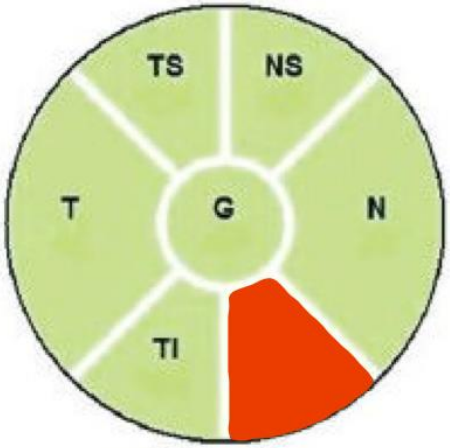


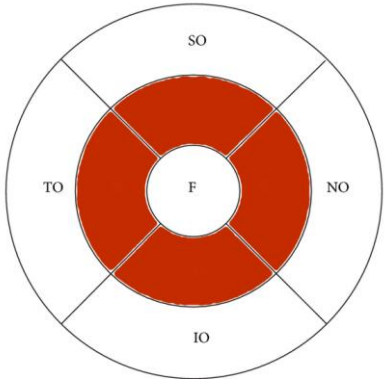
Postuma et al, Brain 2019

Retinal thinning in DLB

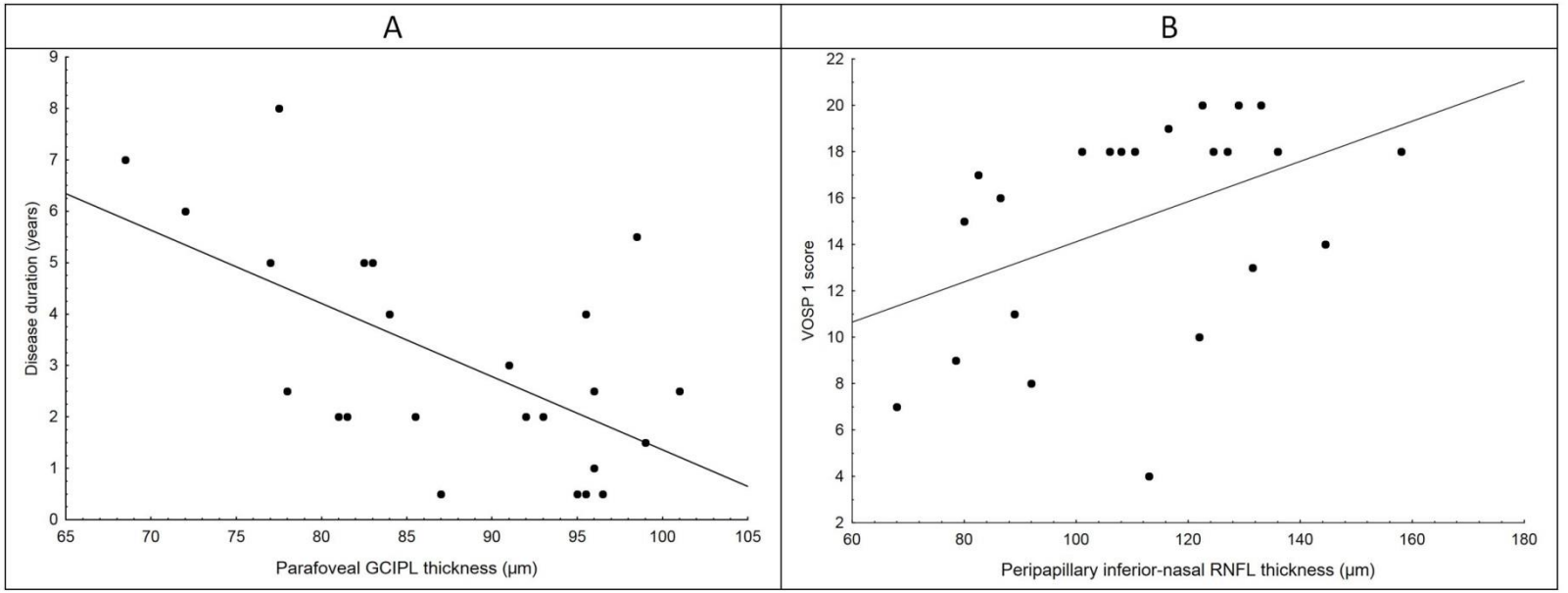
Optical Coherence tomography

Papilla



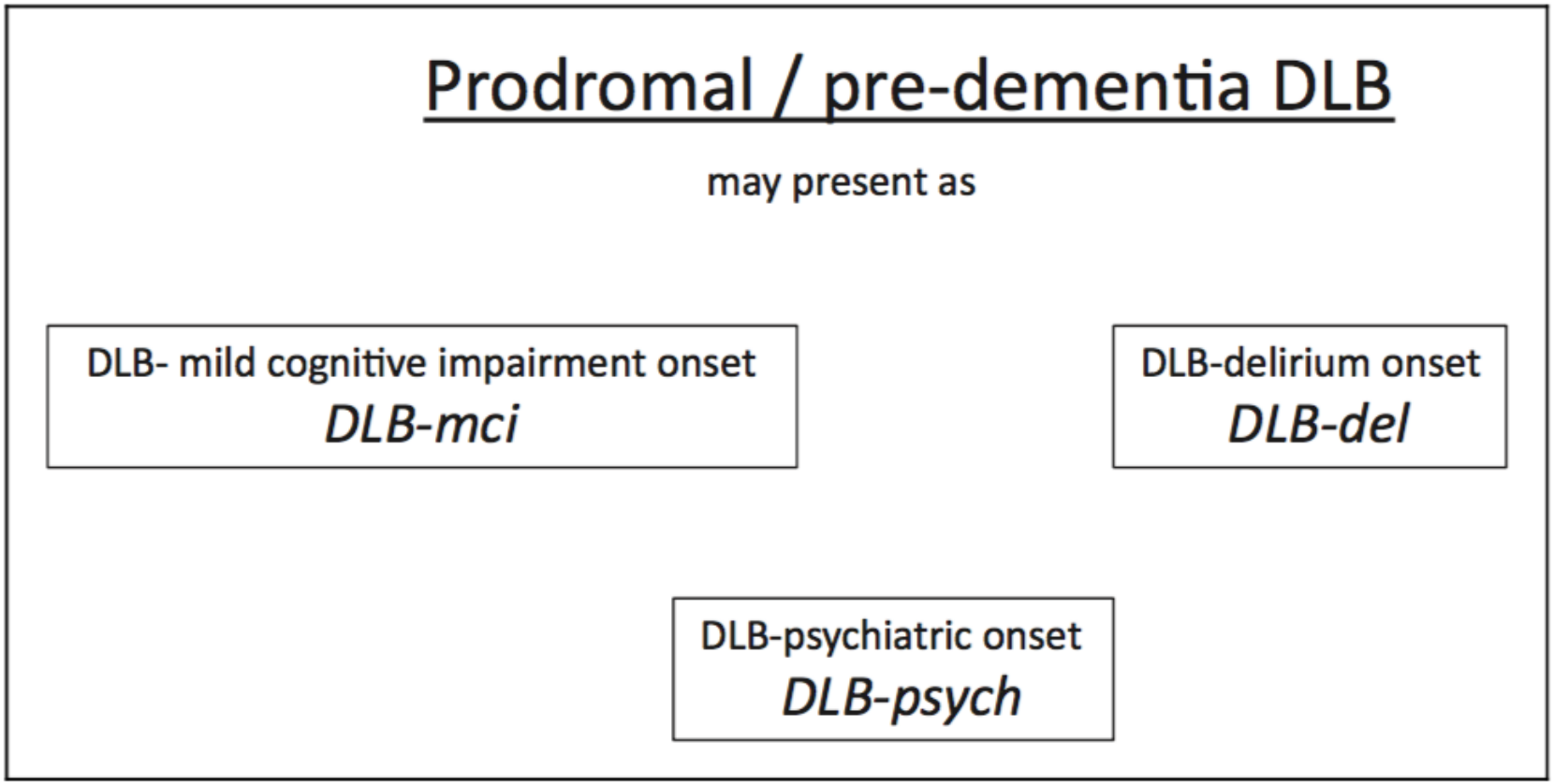


Macula



Fragiacomo, Cagnin, Mov Dis 2019

Prodromal DLB



McKeith et al, 2017

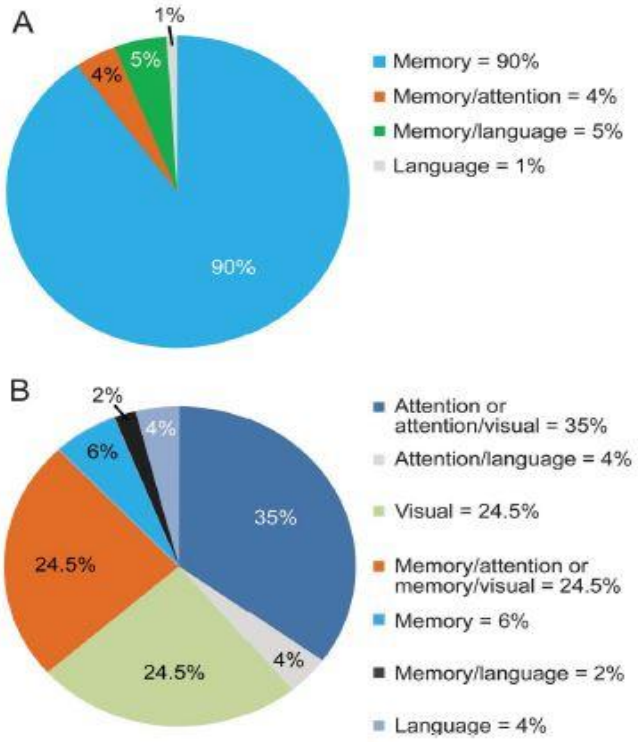
Cognitive impairment in prodromal DLB

Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies

PROGRESSION RATE
incidence/100 person-years

- ✓ **naMCI: 20% DLB**, 1.6% AD
- ✓ **aMCI: 17% AD**, 1.5% DLB

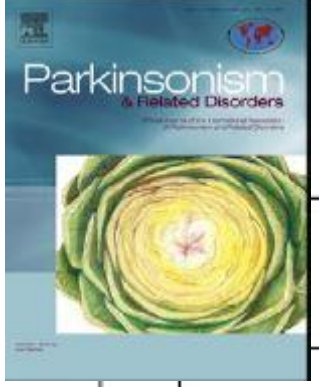
Figure 2 Mild cognitive impairment subtypes and progression to clinically probable Alzheimer disease (A) and probable dementia with Lewy bodies (B)



DIAGNOSIS OF AD

DIAGNOSIS OF DLB

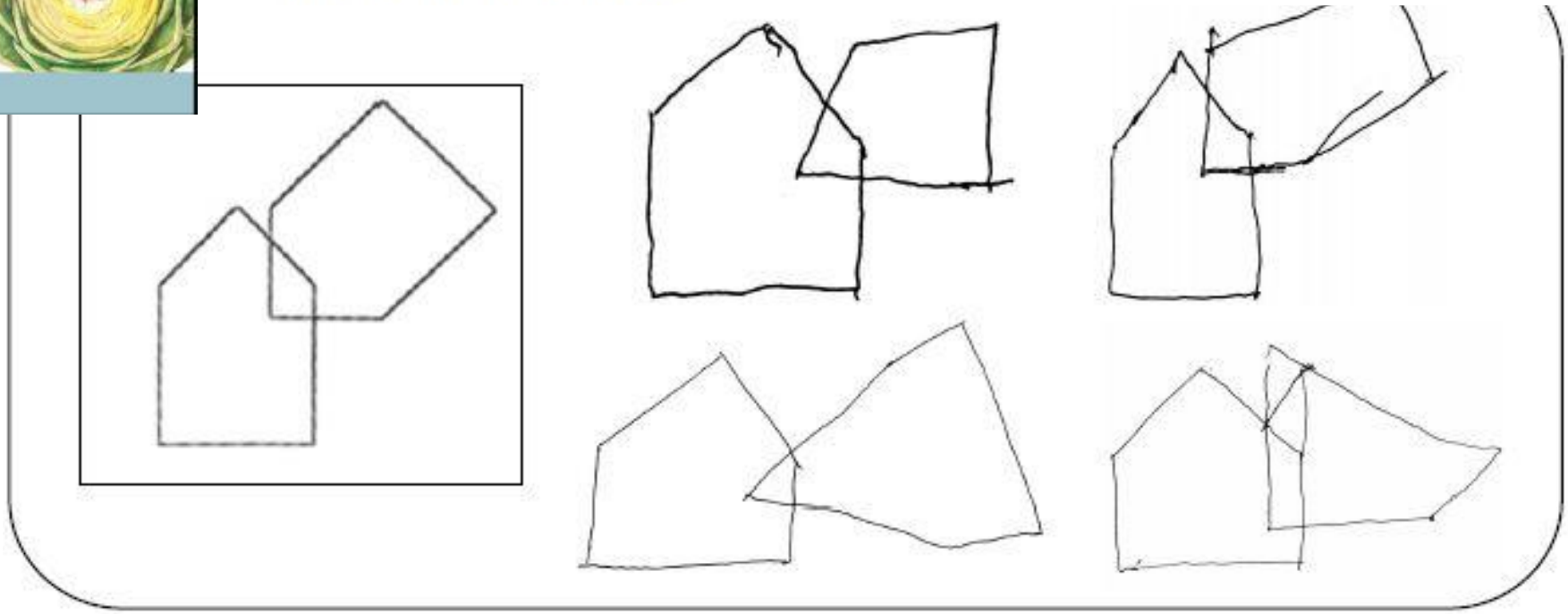
Ferman et al, Neurology 2013



Short communication

High specificity of MMSE pentagon scoring for diagnosis of prodromal dementia with Lewy bodies

Annachiara Cagnin [a, b, *], Cinzia Bussè [a, 1], Nela Jelcic [b, 1], Francesca Gnoato [a], Micaela Mitolo [c], Paolo Caffarra [d]



IMPAIRED NUMBER OF ANGLES

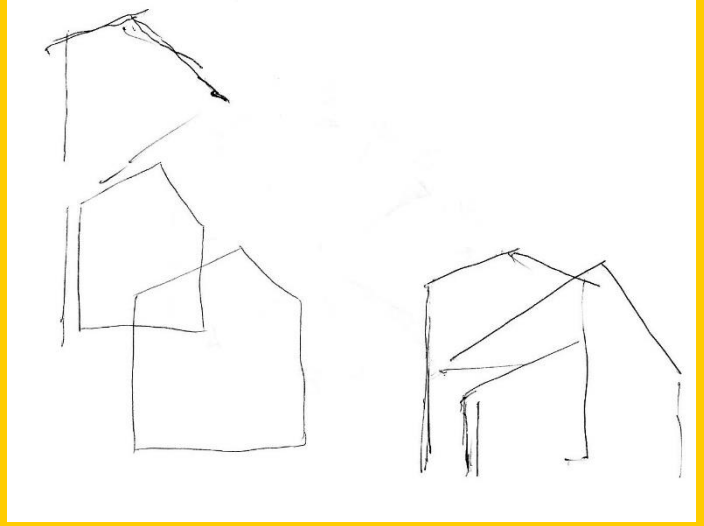
MCI-DLB: 45.1% *versus* MCI-AD: 8.3%, p = 0.005

SENSITIVITY = 41.4%
SPECIFICITY = 91%

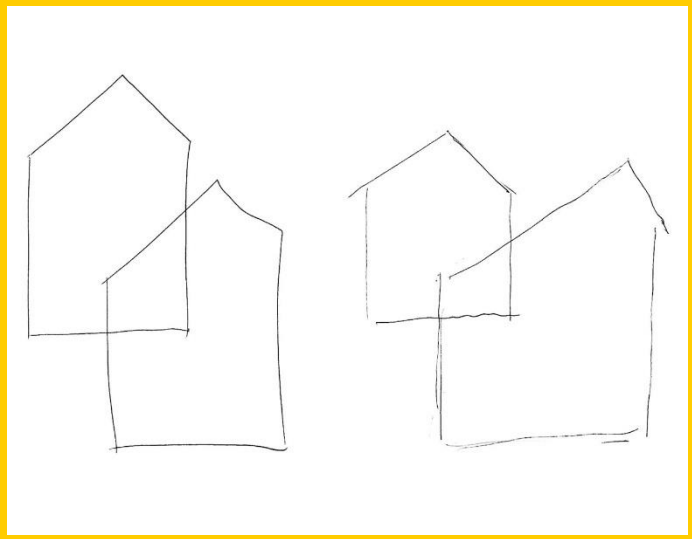
PPV: 86%
NPV: 54%

Neurotransmission in visuospatial performance

2-month time



MMSE: 22/30



MMSE: 30/30

Tryciclic antidepressant
Conventional antypsychotic
Benzodiazepine

SSRI
ChEI

- M; 72 yrs
- RBD

Delirium in the spectrum of DLB

- ✓ Clinical similarities
- ✓ Delirium more common in predementia phase of DLB than AD (Vardy, 2014)
- ✓ Severe cholinergic dysfunction
- ✓ Higher frequency of APOE4 (?)
- ✓ Therapeutic implications (no haloperidol)

core feature

✓ **Complex recurrent visual hallucinations**

DLB-psychiatric onset

Supportive features

- ✓ **…….**
- ✓ **Hallucinations in other modalities**
- ✓ **Sistematized delusions**
- ✓ **Depression-apathy**
- ✓ **…….**

Late-onset Affective disorder

Late-onset psychosis

Treatment refractory

Neuroleptic adverse sensitivity

Sea-monster with 50 tentacles?

R Williams

What's on in DLB?

- ✓ New revised diagnostic criteria
- ✓ Heterogeneity of presentation
- ✓ Definition of prodromal DLB
- ✓ …and hence need of biomarkers

Biomarkers

- Dat scan has well established utility (Se 78%, Sp 90%)
  Only in cases of no or uncertain parkinsonism

- PSG: high likeliwood of synucleopathy but difficult to perform in older demented patients

- MIBG: high specificity

- Need of biomarkers mirroring the molecular pathology (CSF RTQuic?)

ANNALS of Clinical and Translational Neurology
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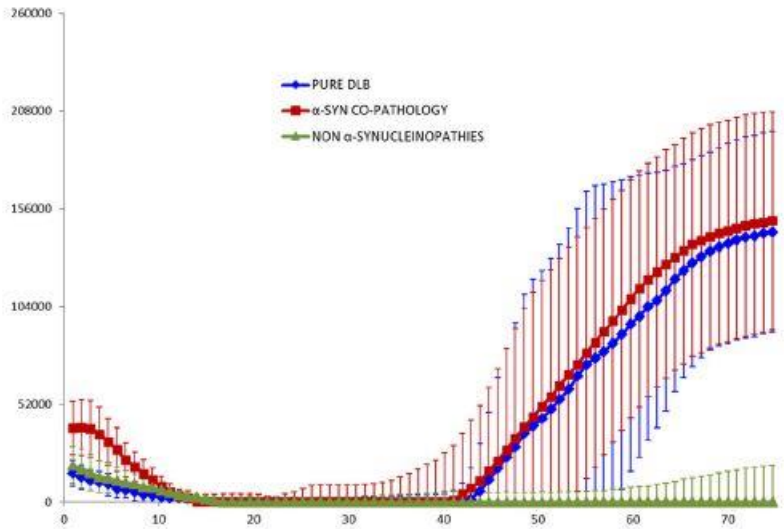
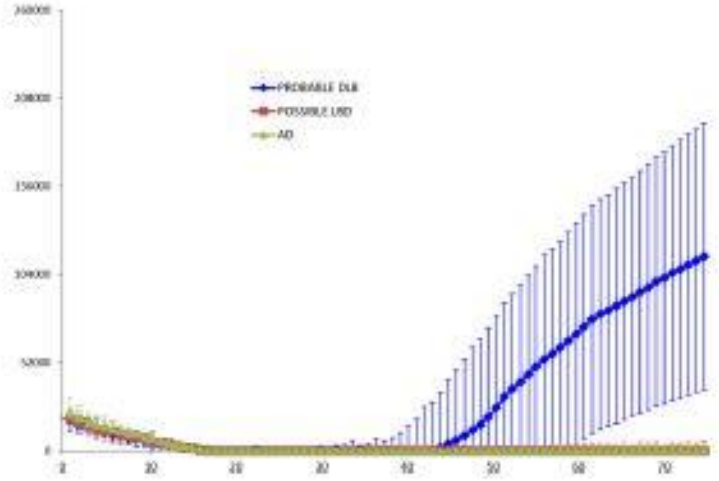
BRIEF COMMUNICATION

α-Synuclein RT-QuIC assay in cerebrospinal fluid of patients with dementia with Lewy bodies

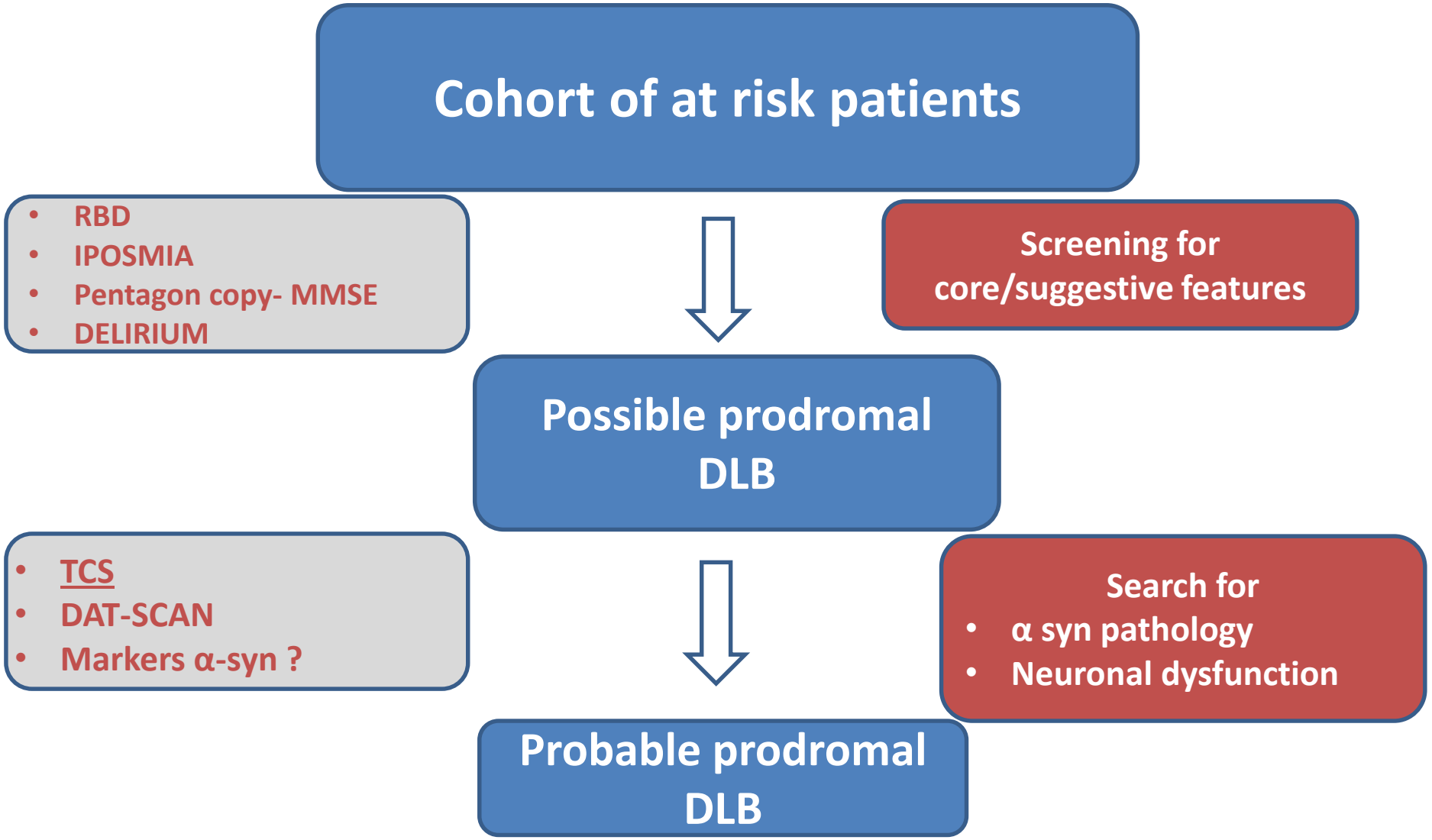
Matilde Bongianni[1], Anna Ladogana[2], Stefano Capaldi[3], Sigrid Klotz[4], Simone Baiardi[5,6], Annachiara Cagnin[7], Daniela Perra[1], Michele Fiorini[1], Anna Poleggi[2], Giuseppe Legname[8], Tatiana Cattaruzza[9], Francesco Janes[10], Massimo Tabaton[11], Bernardino Ghetti[12], Salvatore Monaco[1], Gabor G. Kovacs[4,13,14,15], Piero Parchi[6,16], Maurizio Pocchiari[2] & Gianluigi Zanusso[1]

A





Future scenario



Sea-monster with 50 tentacles

Autopsy validation of ^{123}I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB

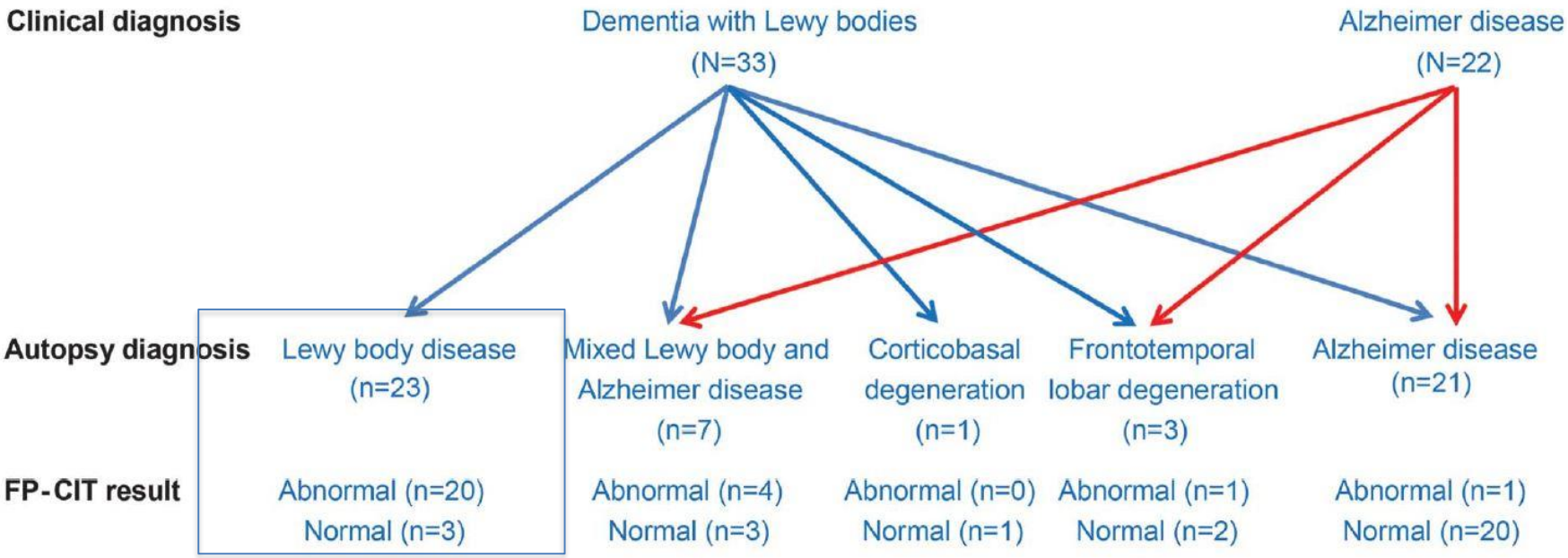
Neurology, 2017

OPEN

"False negative": 10%
"False positive": FTD-parkinsonism

DAT SPECT: SE 80%, SP 92%
CLINICAL DIAGNOSIS: SE 87%, SP 72%

Figure 1 Flowchart showing relationship of clinical diagnosis to autopsy and ^{123}I-FP-CIT imaging findings

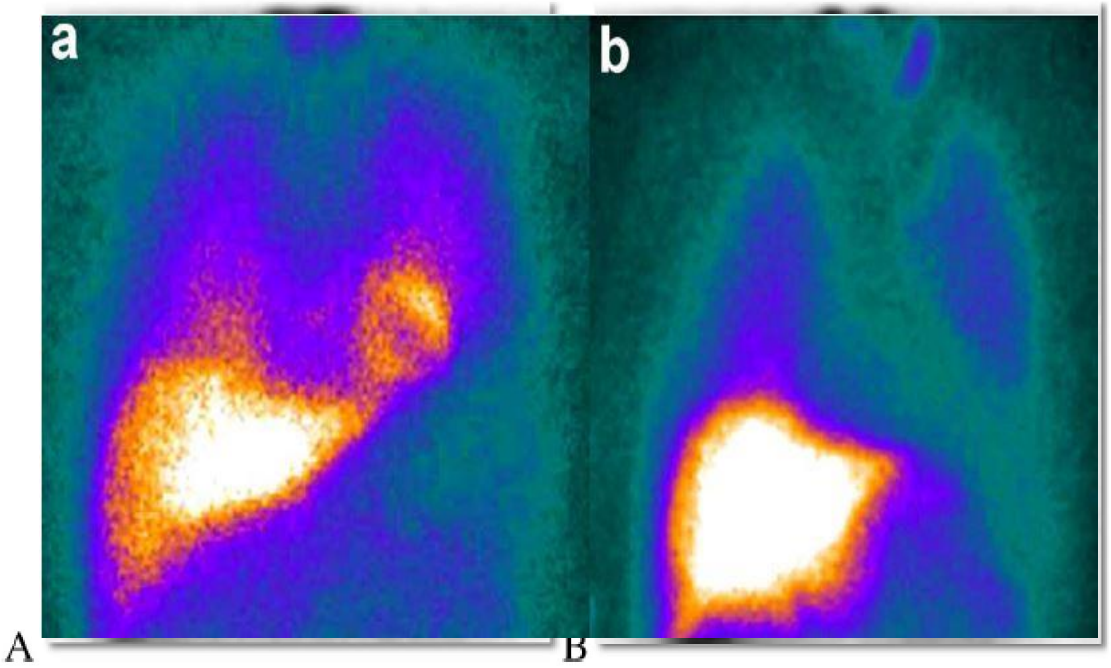


HOW DOES IT LOOK LIKE?

HC

MSA
PSP

AD



PD

Fig. 1. Representative cases of ^{123}I-MIBG myocardial scintigraphy. A: normal control (HM ratio 2.84), B: a case of abnormal low accumulation (HM ratio 1.41). MIBG: meta-iodobenzylguanidine The HM ratio: the heart to mediastinum ratio The cut-off value of delayed MIBG images (4 h after injection of 111 MBq MIBG, depending on uptake-1 [neuronal uptake], reflecting cardiac sympathetic nerve activity) of the HM ratio was 2.0. A reduced HM ratio indicates peripheral noradrenergic depletion.

Ann Neurol. 2016 Sep;80(3):368-78. doi: 10.1002/ana.24717. Epub 2016 Aug 2.

(123) I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography and (123) I-metaiodobenzylguanidine myocardial scintigraphy in differentiating dementia with lewy bodies from other dementias: A comparative study.

Tiraboschi P[1], Corso A[2], Guerra UP[3], Nobili F[4], Piccardo A[5], Calcagni ML[6], Volterrani D[7], Cecchin D[8], Tettamanti M[9], Antelmi L[10], Vidale S[11], Sacco L[11,12], Merello M[13], Stefanini S[13], Micheli A[14], Vai P[15], Capitanio S[15], Gabanelli SV[15], Riva R[16], Pinto P[16], Biffi AM[17], Muscio C[1]; SCILLA Working Group.

Table 3 – Visual assessment findings for myocardial imaging in the differential diagnosis of DLB

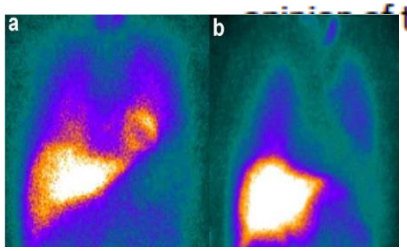
[(123)I]-MIBG myocardial scintigraphy	Sensitivity		Specificity	
	Baseline	*Follow-up*	*Baseline*	*Follow-up*
Rater A	87%	93%	100%	100%
Rater B	84%	90%	100%	100%
Rater C	87%	93%	100%	100%
Overall rating#	87%	93%	100%	100%

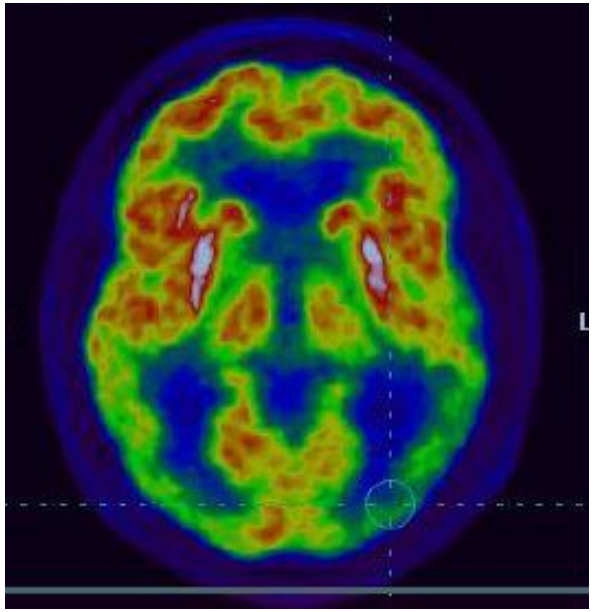
There was complete agreement among the three raters for 56/59 cases. In the remaining three cases, scan assignment to normality or abnormality was based on the opinion of the majority of the raters.

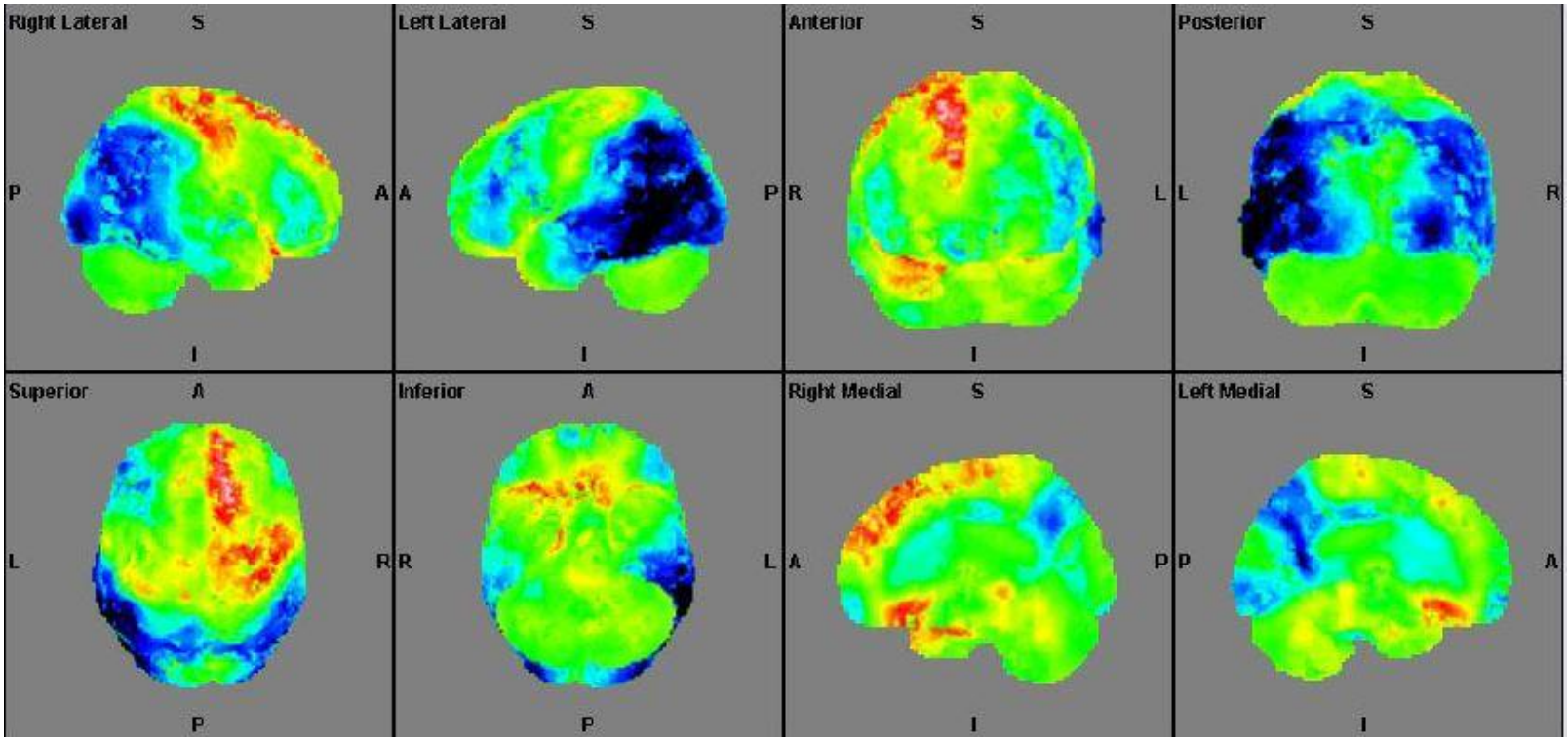
Table 4 – Visual assessment findings for striatal imaging in the differential diagnosis of DLB

[(123)I]-FP-CIT SPECT	Sensitivity		Specificity	
	Baseline	*Follow-up*	*Baseline*	*Follow-up*
Rater D	87%	90%	70%	69%
Rater E	91%	93%	85%	83%
Rater F	84%	87%	74%	72%
Overall rating#	87%	90%	78%	76%

There was complete agreement among the three raters for 52/59 cases. In the remaining seven cases, scan assignment to normality or abnormality was based on the opinion of the majority of the raters.




L


Right Lateral
S
P
A
I
Left Lateral
S
A
P
I
Anterior
S
R
L
I
Posterior
S
L
R
I
Superior
A
L
R
P
Inferior
A
R
L
P
Right Medial
S
A
P
I
Left Medial
S
P
A
I

Cingulate Island Sign

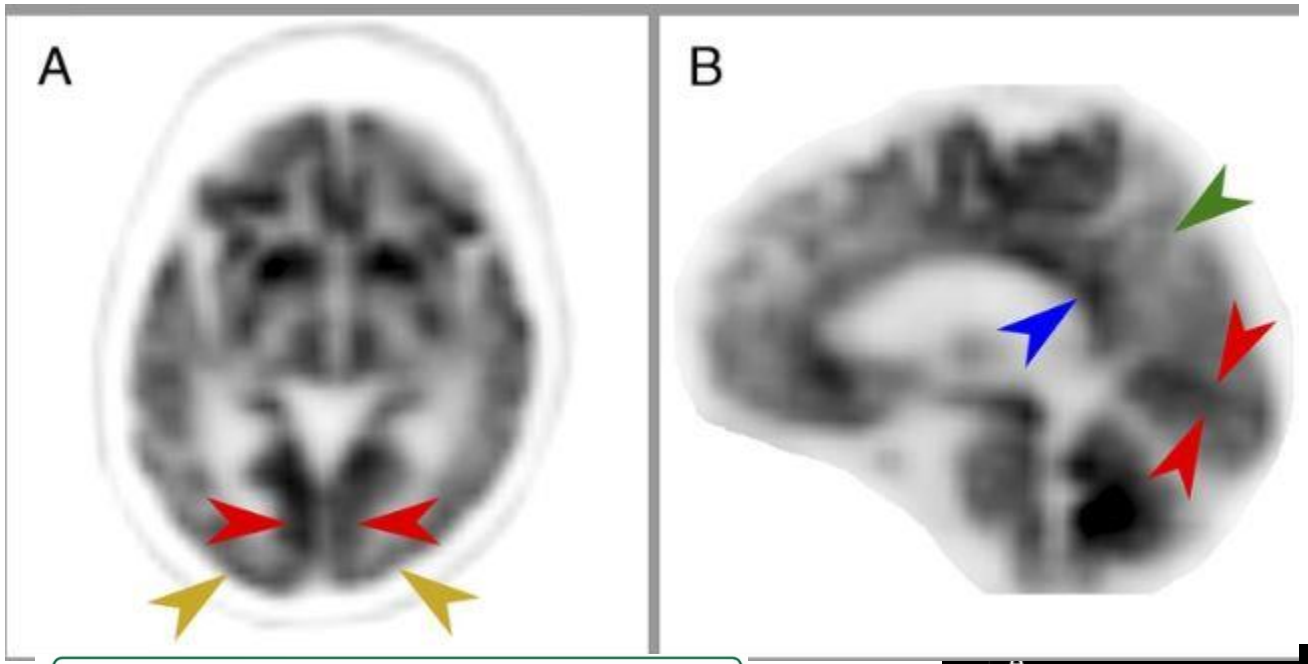
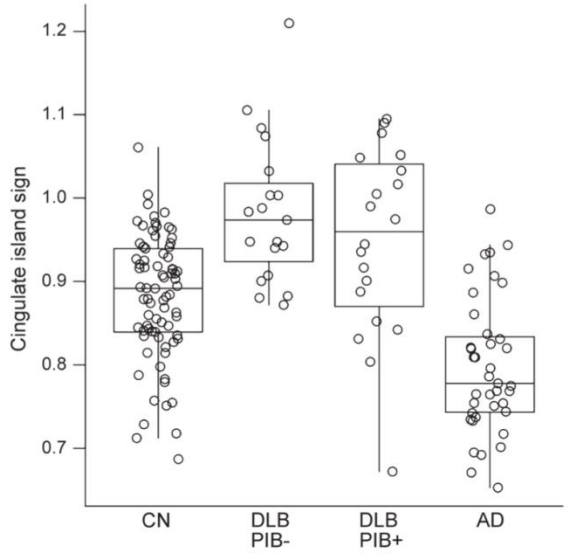
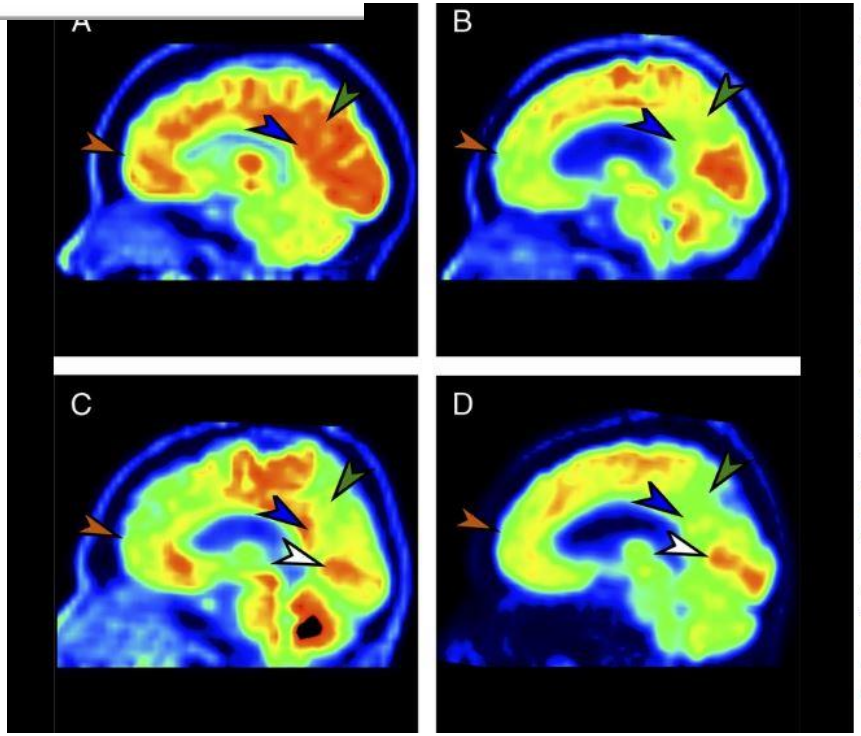


Figure 1 Box plots of the cingulate island sign ratio among the patient groups



AD = Alzheimer disease; CN = cognitively normal; DLB = dementia with Lewy bodies; PiB = Pittsburgh compound B; PiB− = PiB negative; PiB+ = PiB positive.

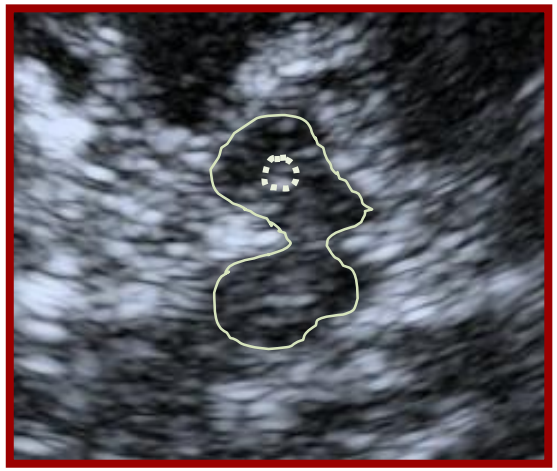


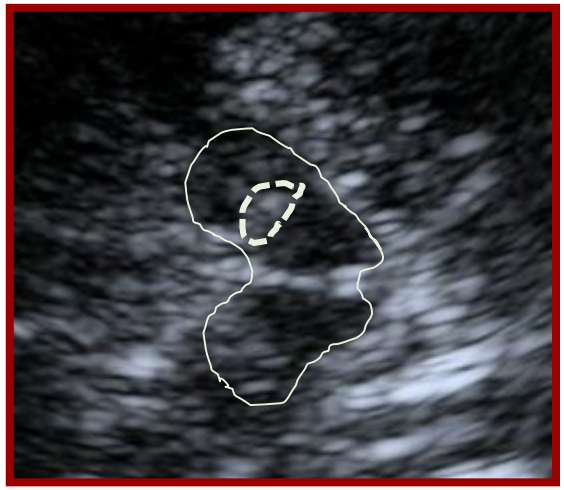
Kantarci, Neurology 2017

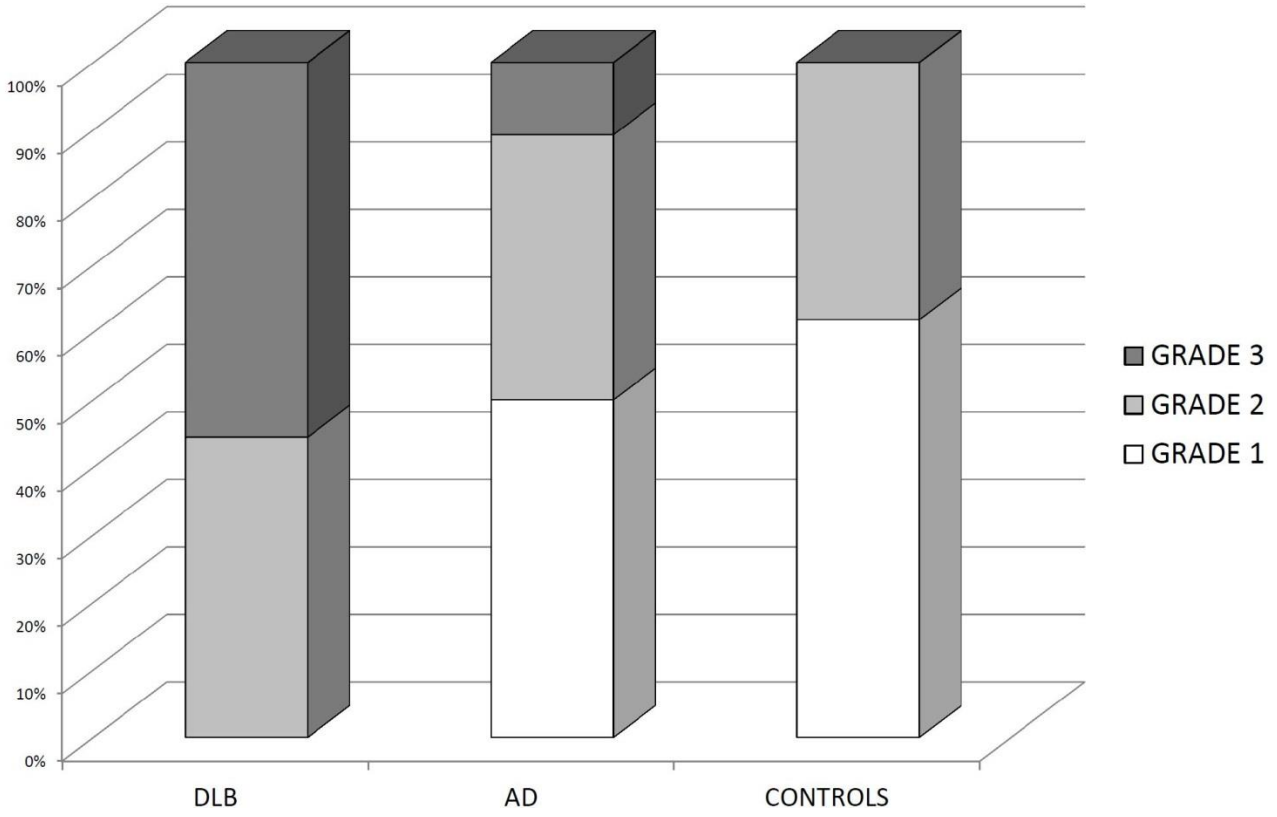
ORIGINAL ARTICLE

Accuracy of transcranial brain parenchyma sonography in the diagnosis of dementia with Lewy bodies

S. Favaretto[a], U. Walter[b], C. Baracchini[a], S. Pompanin[a], C. Bussè[a], G. Zorzi[a], M. Ermani[a] and A. Cagnin[a,c]







Motor cluster

- ✓ *"One of the motor signs of Parkinson disease among bradykinesia, rigidity,* ***rest tremor****."*

What's on in DLB?

- ✓ New revised diagnostic criteria
- ✓ Heterogeneity of presentation
- ✓ Definition of prodromal DLB
- ✓ …and hence need of biomarkers

Visual Hallucinations

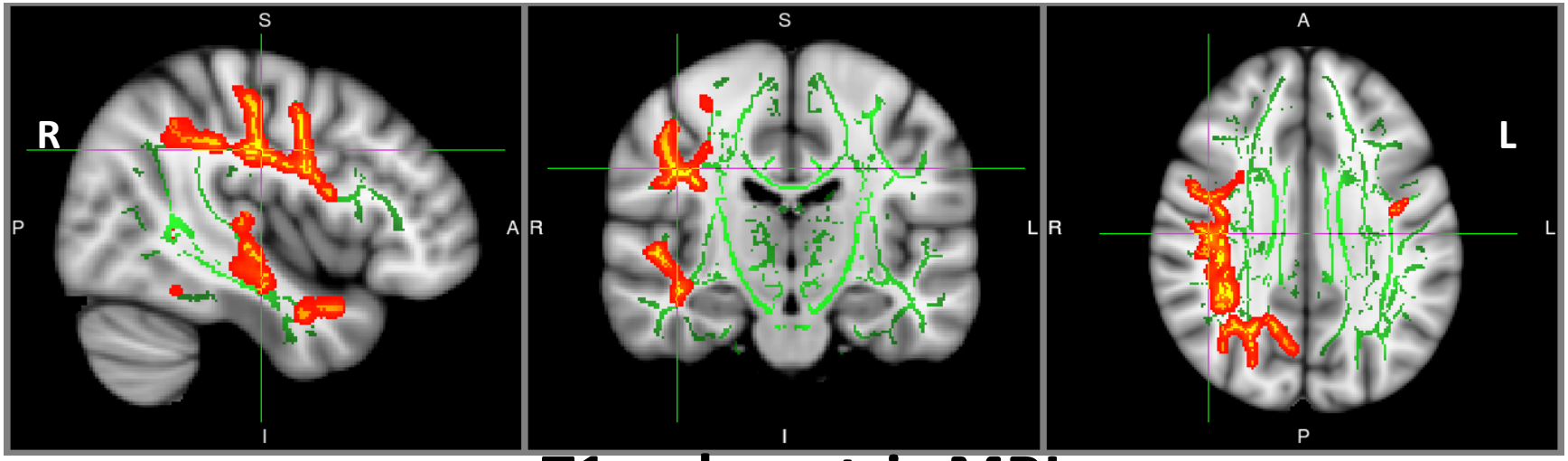
- Recurrent complex VH (human faces, animals)
- Preserved environment
- Poor/lack insight
- Coping strategies

- Pre-hallucinatory episodes:
  - o Feeling of presence or of passage
  - o Visual illusions

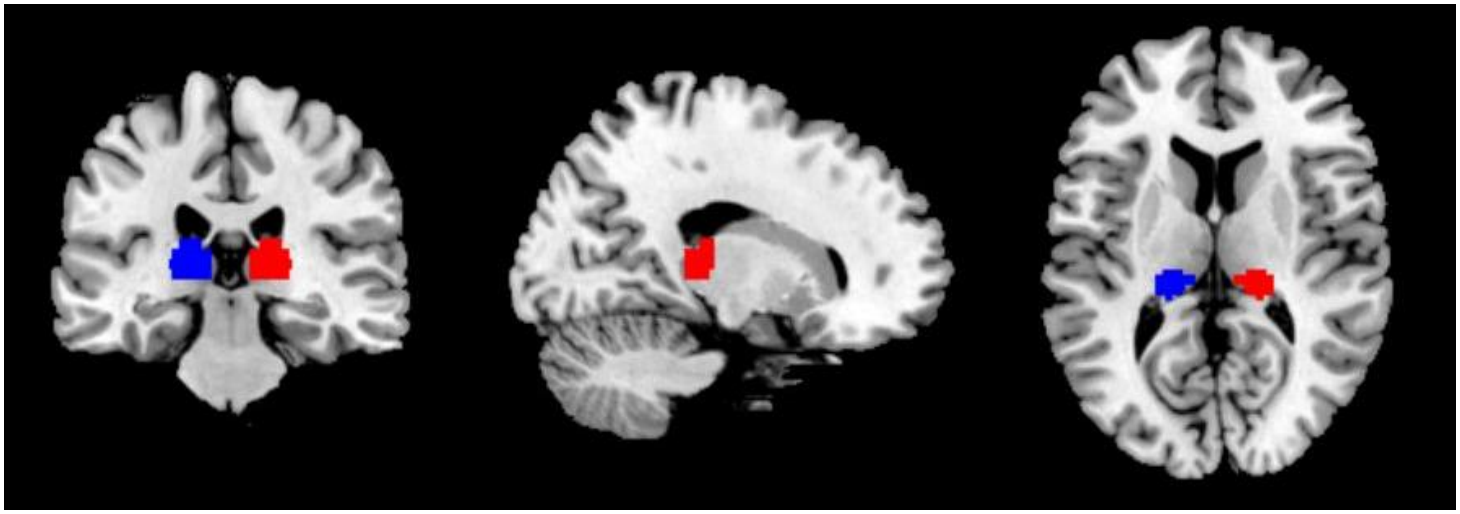
- Secondary related delusions

Anatomical correlates of VH

DTI-MRI

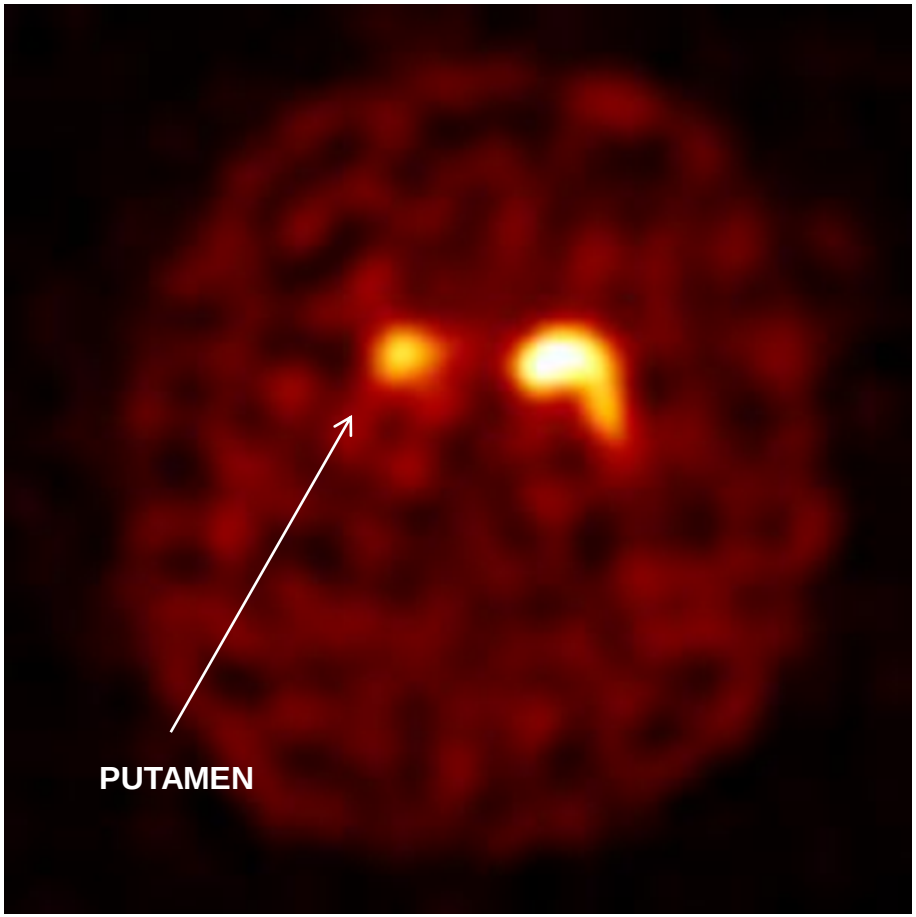


T1-volumetric MRI

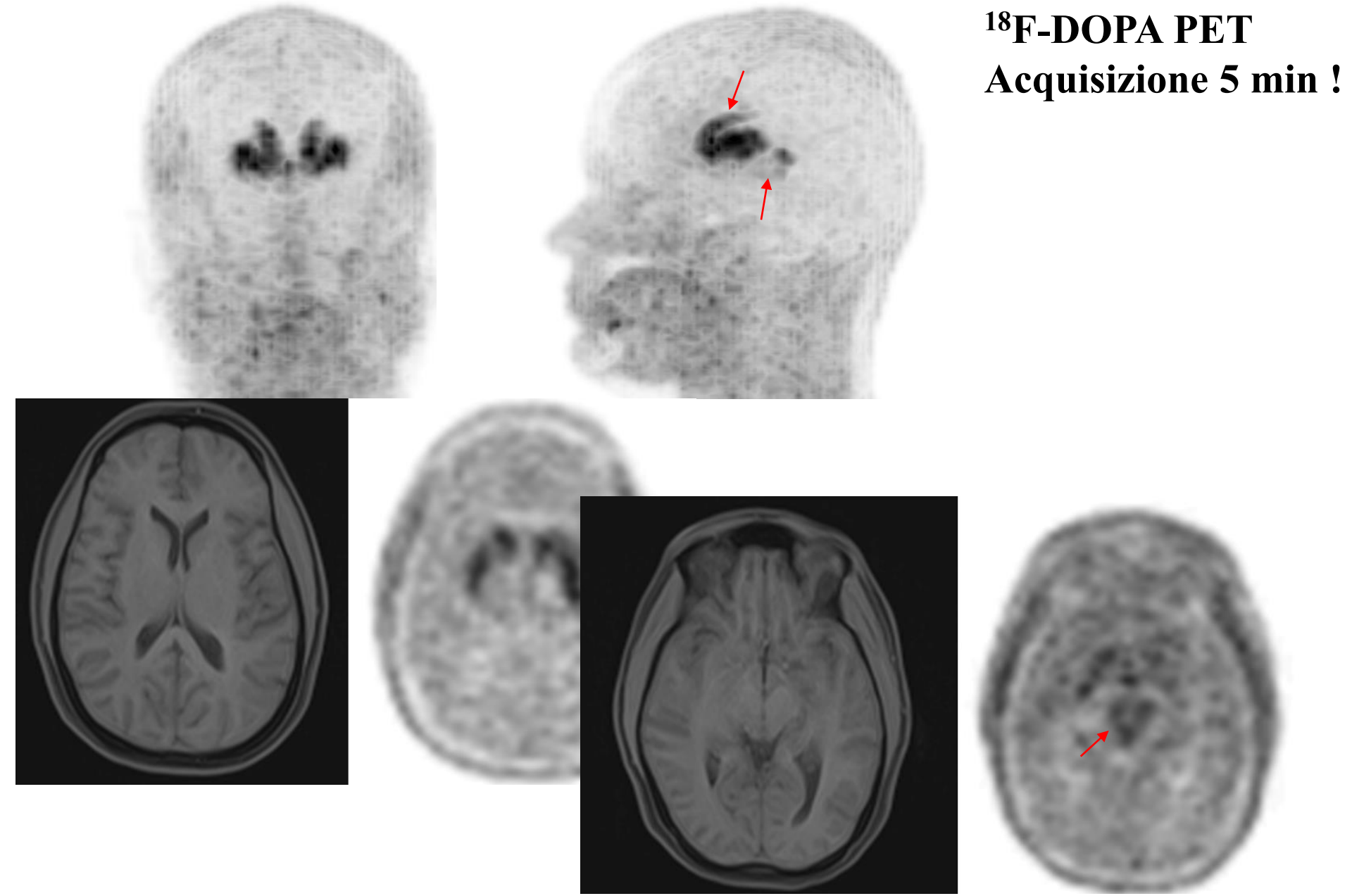


Cagnin et al, submitted

In PD the lateral part of SN always degenerates first
=
Preferential loss in putamen relative to caudate

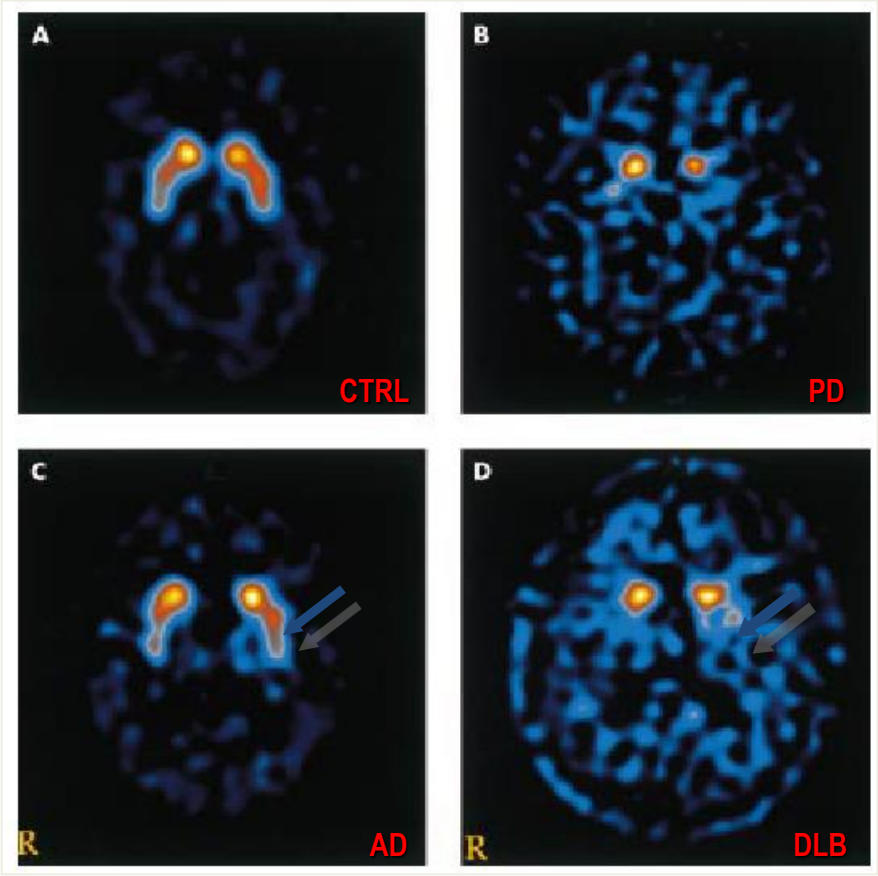


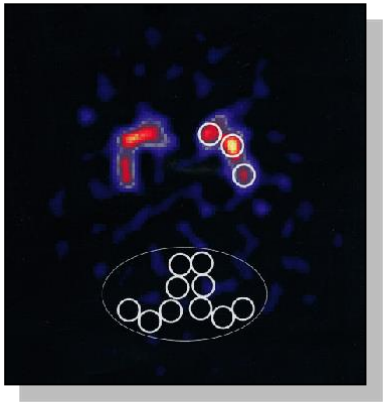
“From comma to full stop !”

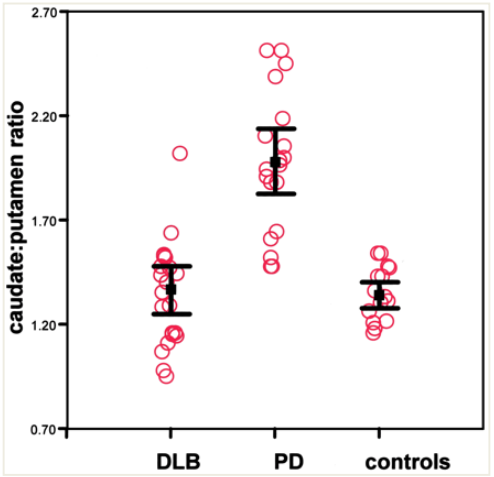

18F-DOPA PET
Acquisizione 5 min !

DAT scan in DLB

^{123}I-FP-CIT scans







Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand

Z Walker, D C Costa, R W H Walker, K Shaw, S Gacinovic, T Stevens, G Livingston, P Ince, I G McKeith, C L E Katona

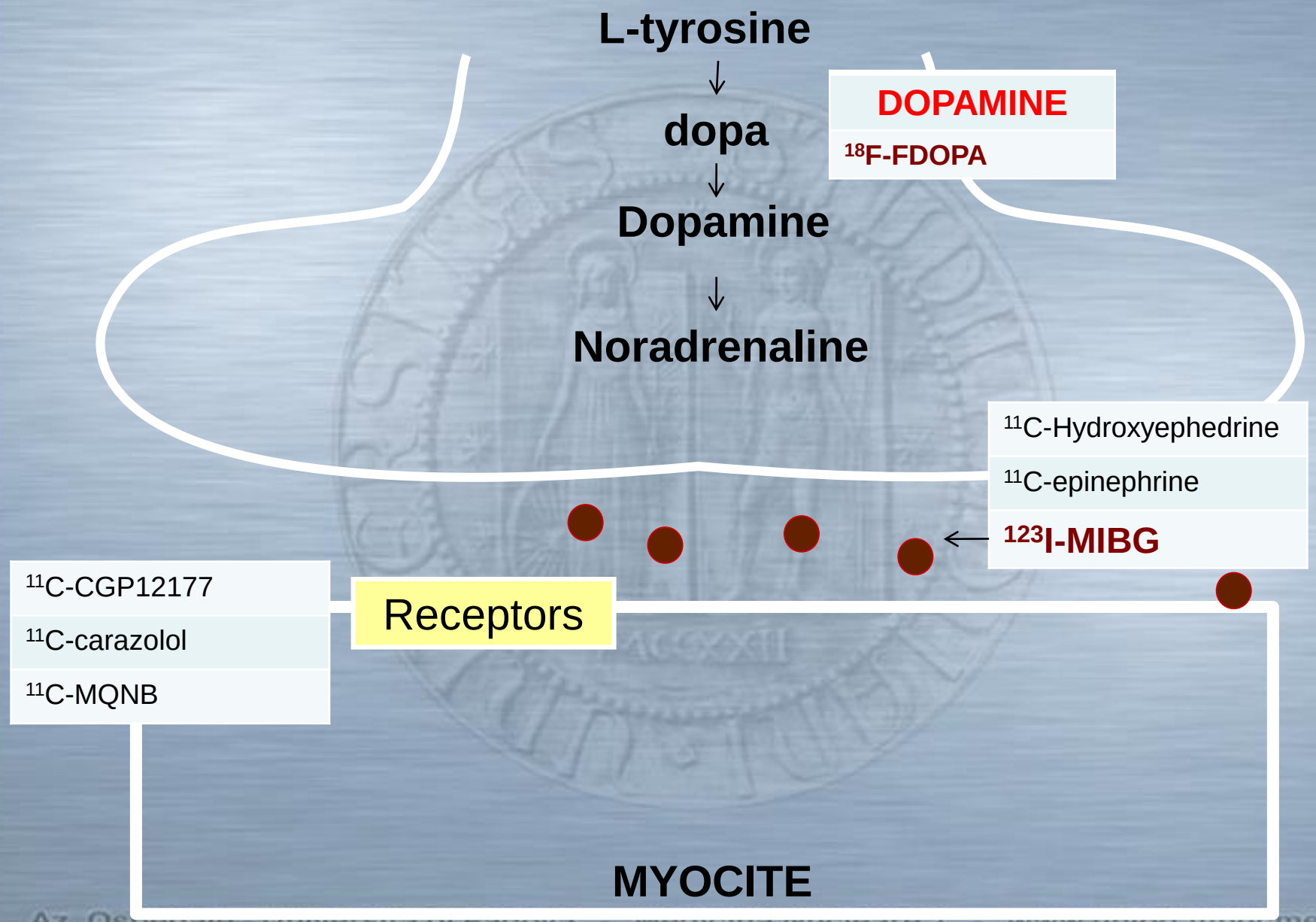
J Neurol Neurosurg Psychiatry 2002;**73**:134–140

Walker, Neurology 2004

“INDICATIVE BIOMARKER”

^{123}I-MIBG

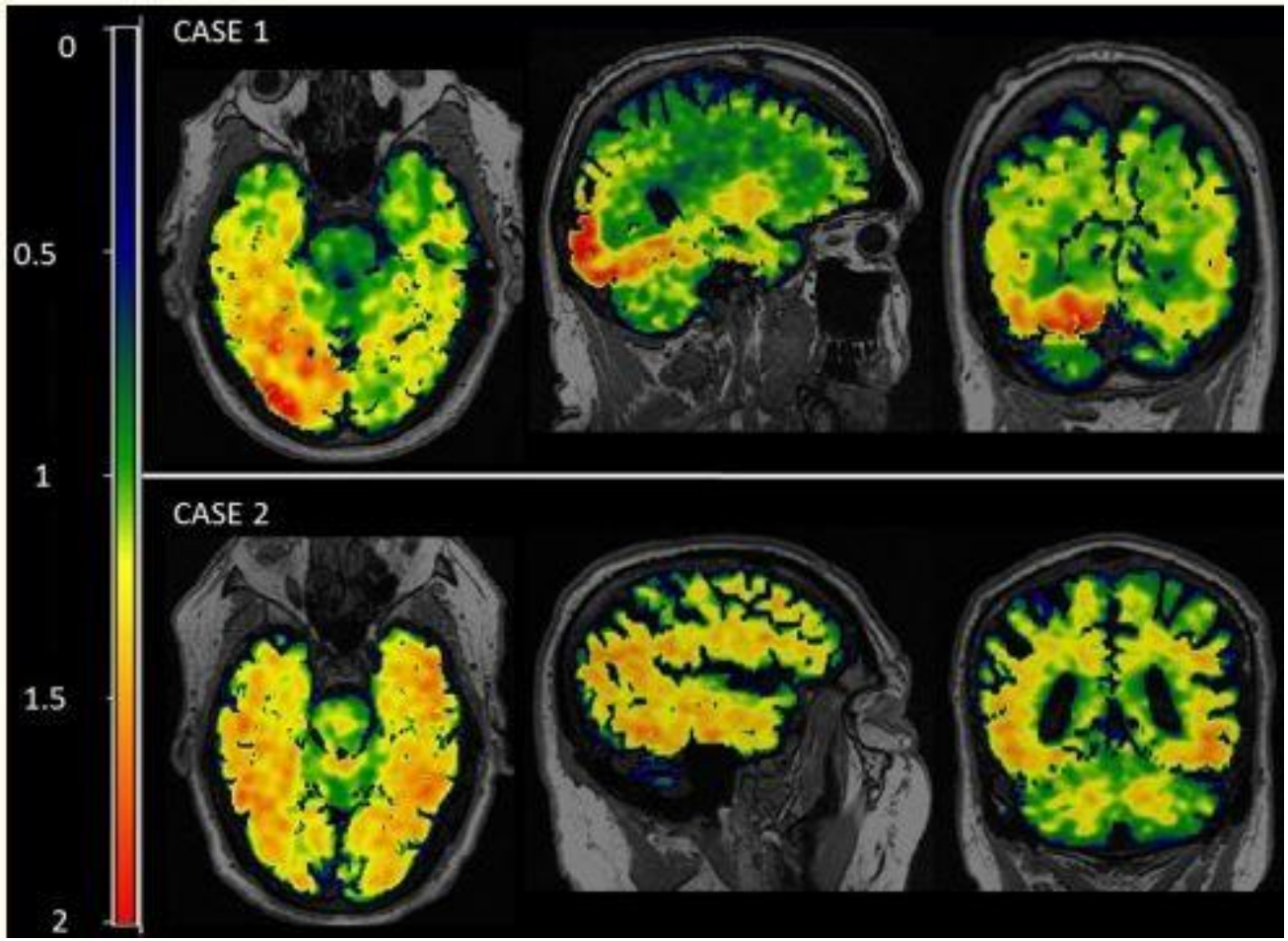
TARGETS FOR DOPAMINERGIC LIGANDS



Atypical pattern of tau deposition

DLB Temporo-parietal regions

Amy +

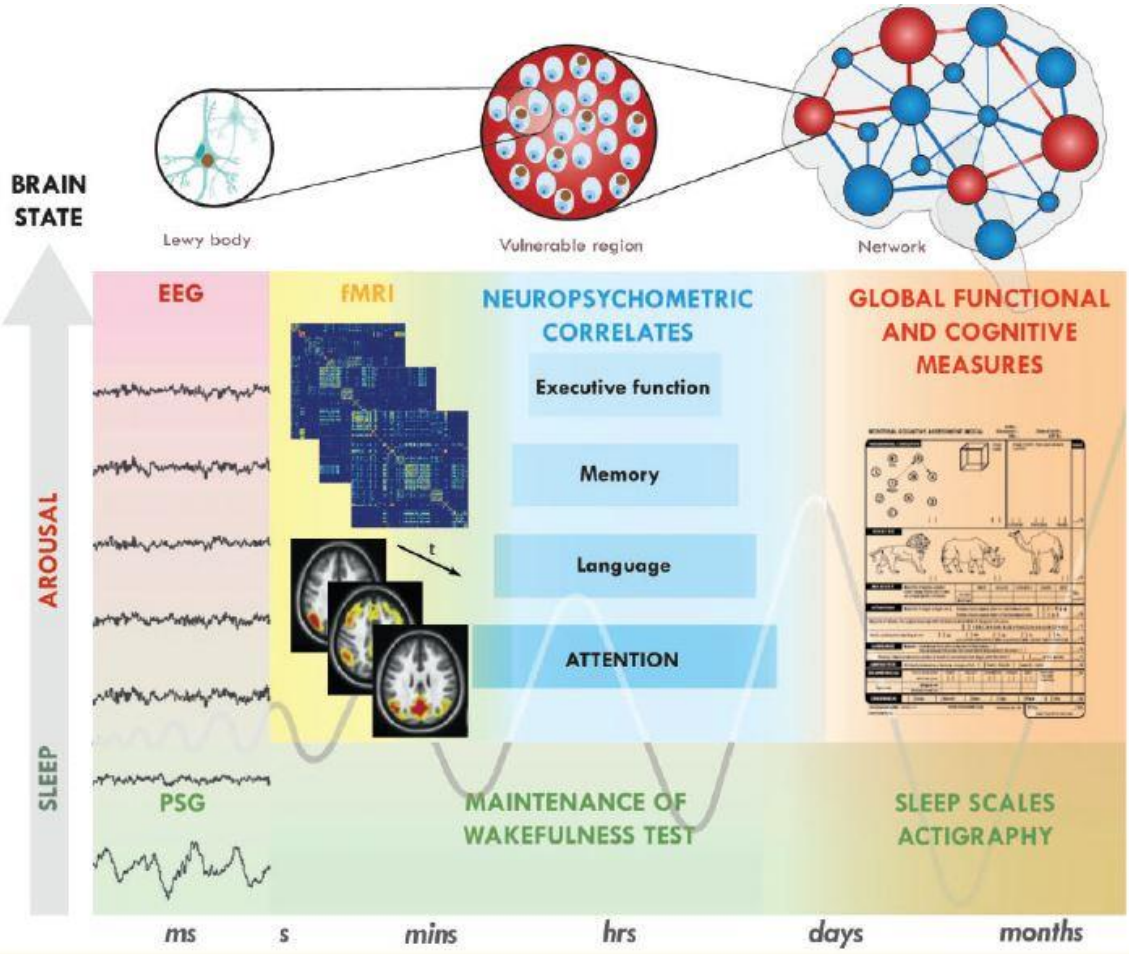


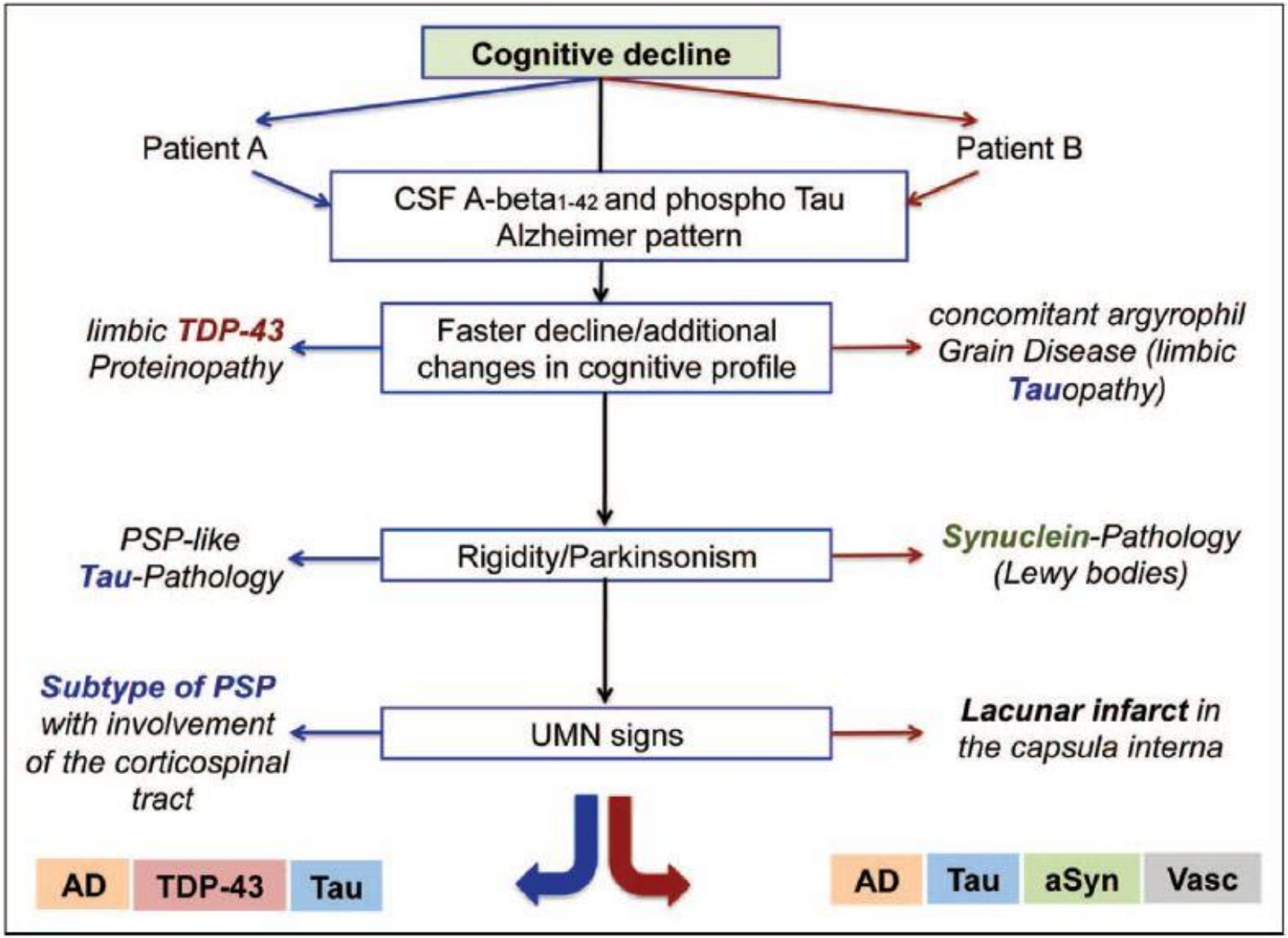
AV 1451 TAU +

Amy -

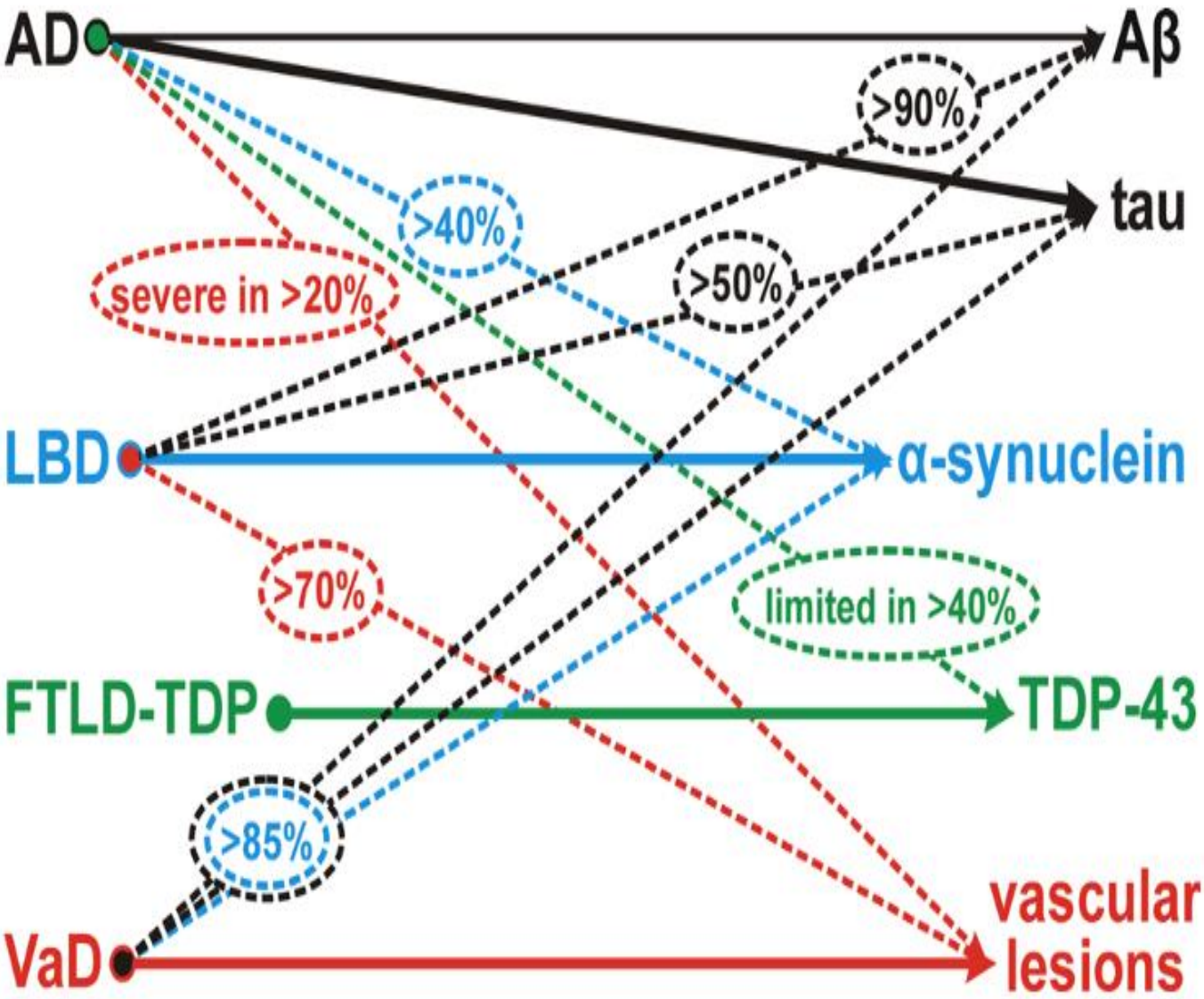
AV 1451 TAU +

Kantarci, Ann Neurol 2017


BRAIN STATE
Lewy body
Vulnerable region
Network
EEG
FMRI
NEUROPSYCHOMETRIC CORRELATES
GLOBAL FUNCTIONAL AND COGNITIVE MEASURES
Executive function
Memory
Language
ATTENTION
t
AROUSAL
SLEEP
PSG
MAINTENANCE OF WAKEFULNESS TEST
SLEEP SCALES ACTIGRAPHY
ms
s
mins
hrs
days
months

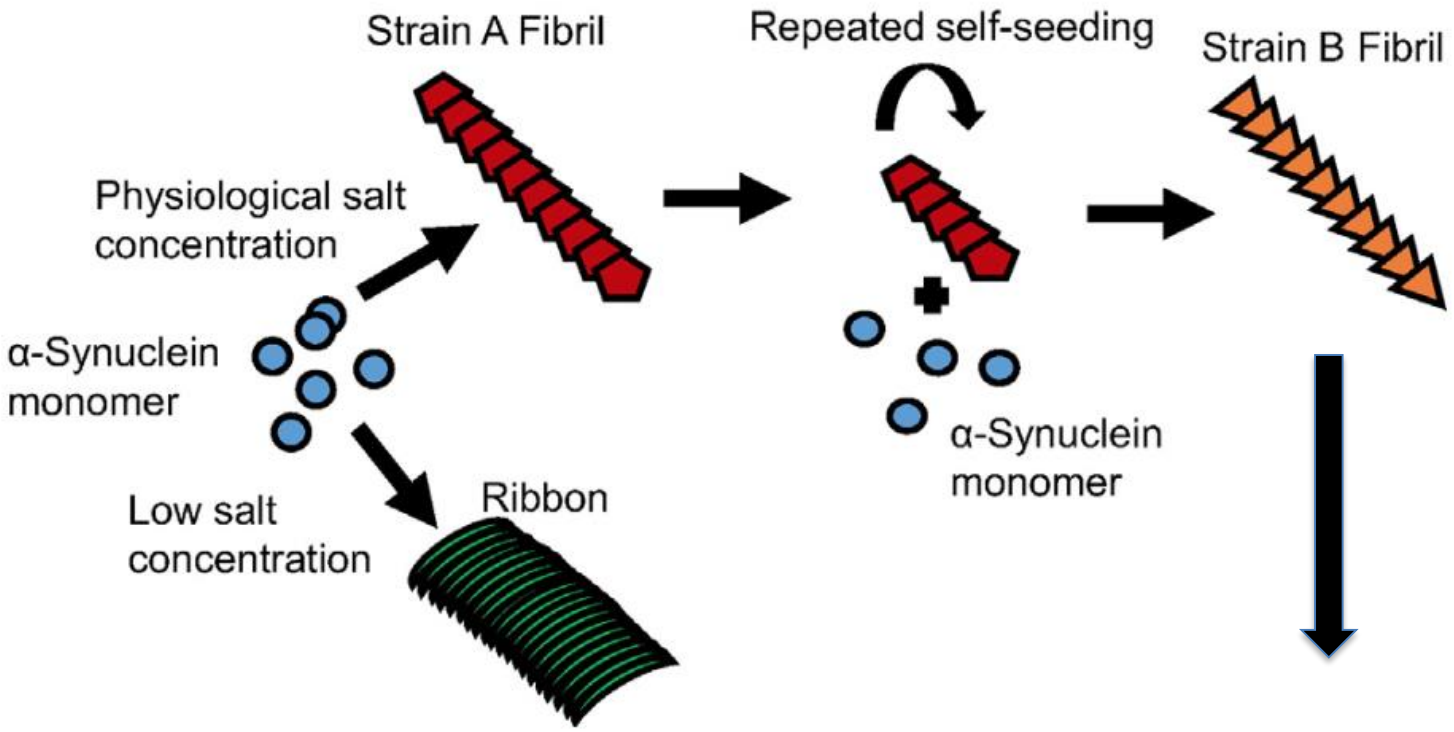

Cognitive decline
Patient A
Patient B
CSF A-beta1-42 and phospho Tau
Alzheimer pattern
limbic TDP-43
Proteinopathy
Faster decline/additional
changes in cognitive profile
concomitant argyrophil
Grain Disease (limbic
Tauopathy)
PSP-like
Tau-Pathology
Rigidity/Parkinsonism
Synuclein-Pathology
(Lewy bodies)
Subtype of PSP
with involvement
of the corticospinal
tract
UMN signs
Lacunar infarct in
the capsula interna
AD
TDP-43
Tau
AD
Tau
aSyn
Vasc

Kovacs, 2019

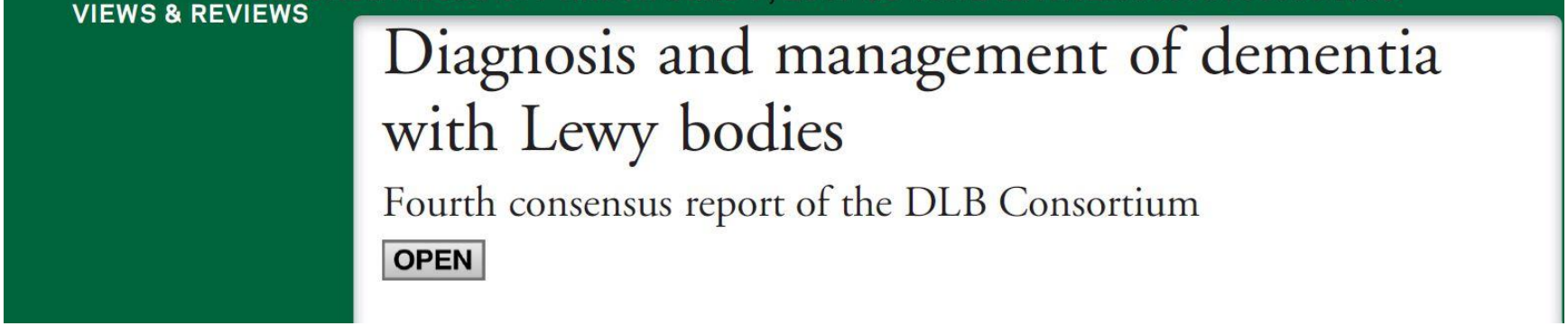


Jellinger, 2015

a-synuclein strains



Cross seed with other proteins



Supportive features

- Severe sensitivity to antipsychotics
- Postural instability
- Falls/syncope
- Transient episodes unconsiousness
- Autonomic dysfunction
- Hypersomnolence
- Hyposmia
- Hallucinations in other modalities
- Systematized delusions
- Apathy-anxiety-depression

Supportive biomarkers

- Relative preservation MTL
- General low PET uptake with reduced occipital activity +/- cingulate island sign
- Posterior slow-wave activity on EEG with periodic fluctuations