Biomarkers for LBD

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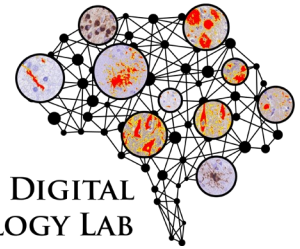

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Disclosures

- LBDA Scientific Advisory Board (non-compensated).
- Legal consultation regarding cognitive impairment.
- Research funding: NIH/NINDS, Brightfocus Foundation and Penn Institute on Aging.

Overview

- Biomarkers for α-synucleinopathy
- Interpretation of AD biomarkers in LBD

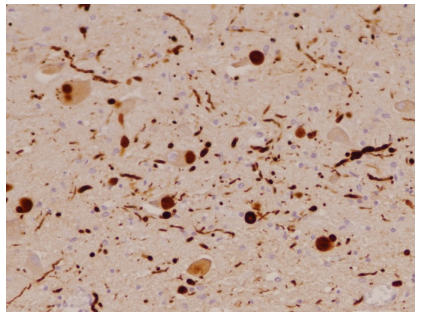
Lewy body diseases: Clinicopathological Diagnosis

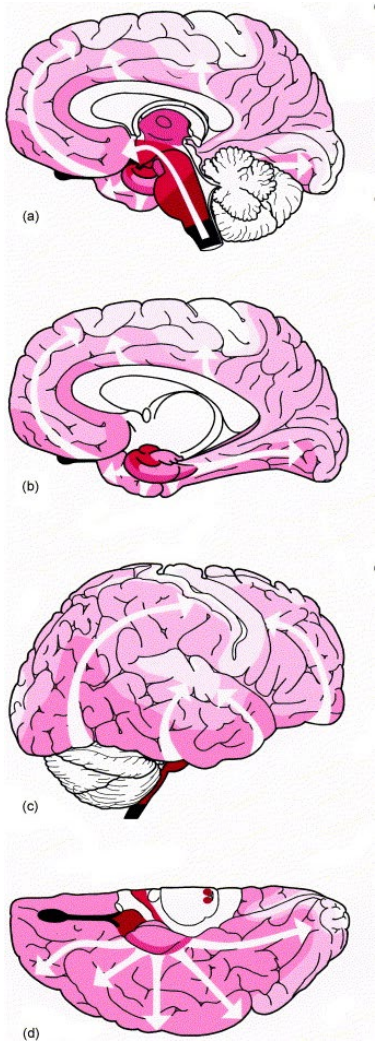
- Lewy body diseases (PD/PDD/DLB):

  - α-synuclein LBs/LNs.
  - Dementia is common in PD[1] and can resemble DLB[2].
  - Shared prodromal (RBD)[3] and genetic features (*SNCA*[4], *GBA*[5]).

1. Aarsland et al Arch Neurol 2003; 2. Emre et al, *Mov Do* 2017; 3. Boeve et al *Mov Do 2001*; 4. Polymeropoulos et al *Science* 1997; 5. Tsuang et al *Neurology* 2012.

α-SYN LB





From Braak et al, *Neurobiol aging* 2002

Lewy body diseases: Clinicopathological Diagnosis

	DLB	PDD
Essential Features	Dementia before or < 1 year after motor Parkinsonism (attention, executive, visuospatial > memory, language)	Dementia in setting of established PD (>1 year) (attention, executive, visuospatial > memory, language)
Core Features	Cognitive fluctuations Visual hallucinations Spontaneous Parkinsonism (>1 feature) REM sleep behavior disorder	
Associated/ Suggestive Features	Severe Neuroleptic sensitivity Postural Instability Repeated falls Syncope/ Transient LOC Autonomic Dysfunction Depression Hallucinations in other modalities Systematized delusions	Apathy Depression/anxiety Hallucinations Delusions Excessive daytime sleepiness
Indicative Biomarkers	Low Dopamine transporter uptake MIBG myocardial scintigraphy Sleep study confirmation REM SBD	

Adapted From McKeith et al Neurology 2017, Emre et al Mov DO 2007

DLB Clinical Criteria 2017

	DLB
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Core Features	Cognitive fluctuations Visual hallucinations Spontaneous Parkinsonism (>1 feature) REM sleep behavior disorder
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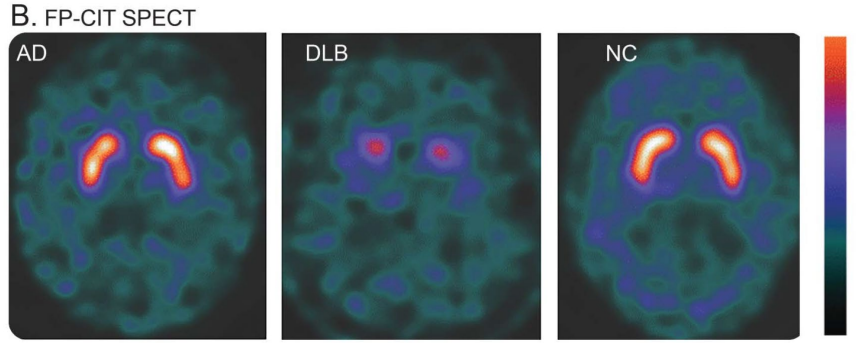

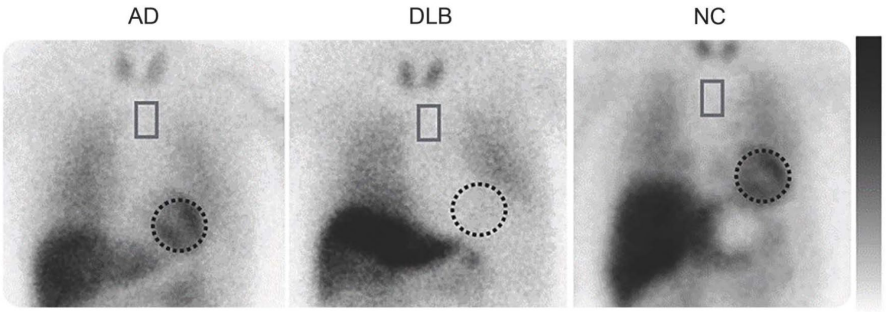

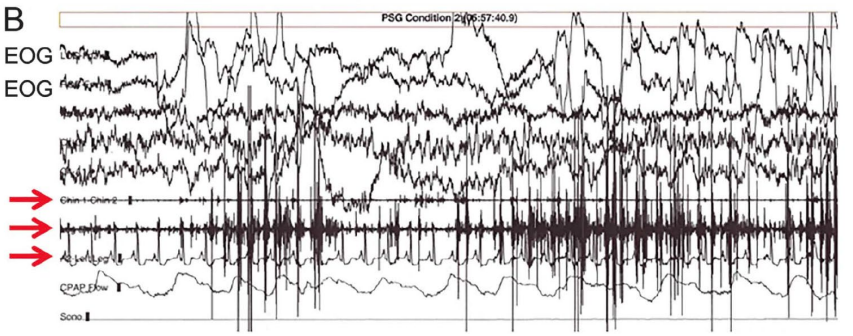

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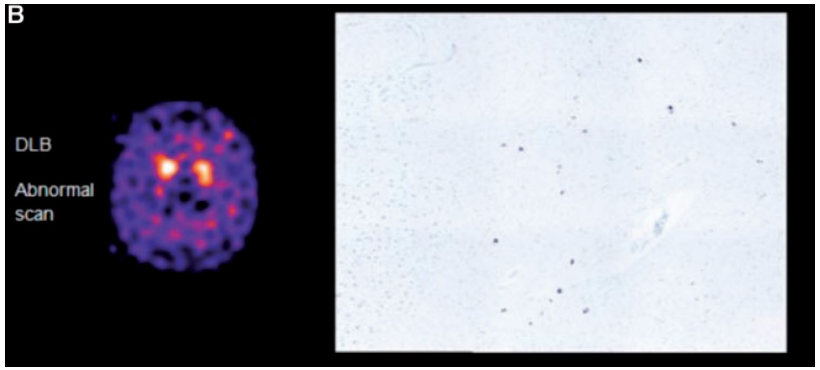
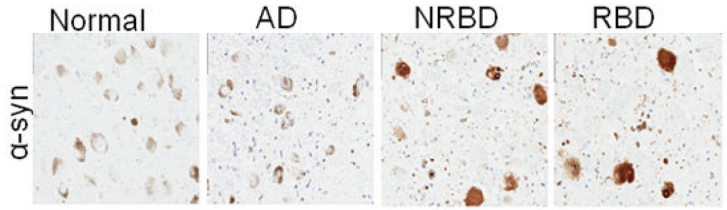
Adapted From McKeith et al Neurology 2017

Pathological basis for LBD Biomarkers

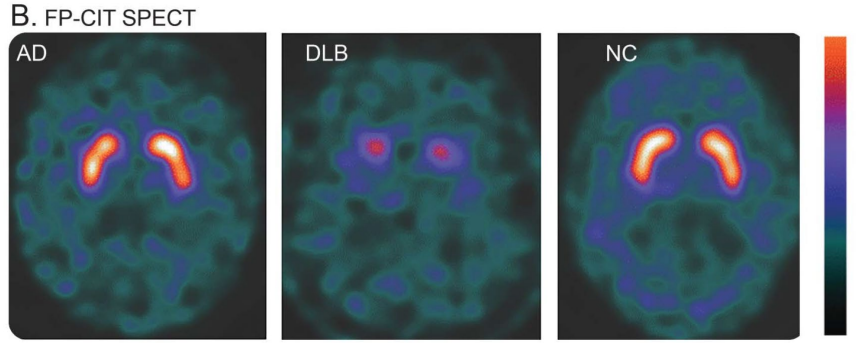


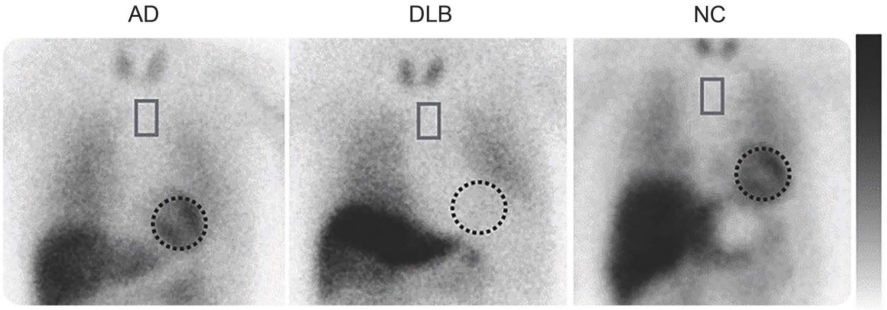
From Colloby et al, *Brain* 2012

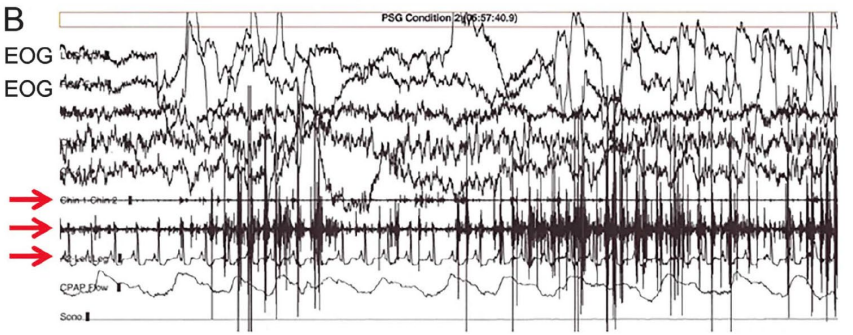
From Orimo et al, *Acta Neuropathol* 2005



From Dugger et al, *Neuropathol Appl Neurobiol. 2012*







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Detecting Prodromal LBD

Table 1. Clinical Features That Have Been Suggested as Indicative of Early LB Disease.

Early symptoms (typically 5-15 years pre-dementia)
Decreased sense of smell
REM sleep behavior disorder
– Nightmares
– Crying or shouting during sleep
– Limb movements during sleep
Constipation
Dizziness on standing
Urinary incontinence
Increased saliva
Increased sweating
Intermediate symptoms
Delirium: provoked or unexplained
Late onset psychiatric disorder
– Psychosis
– Depression
Later symptoms
Cognitive impairment (nonamnestic mild cognitive impairment)
Visual hallucinations, illusions, and misconceptions
Parkinsonism

Abbreviations: LB, Lewy body: REM, rapid eye movement.

From McKeith et al, *J GerPsych Neurol* 2016

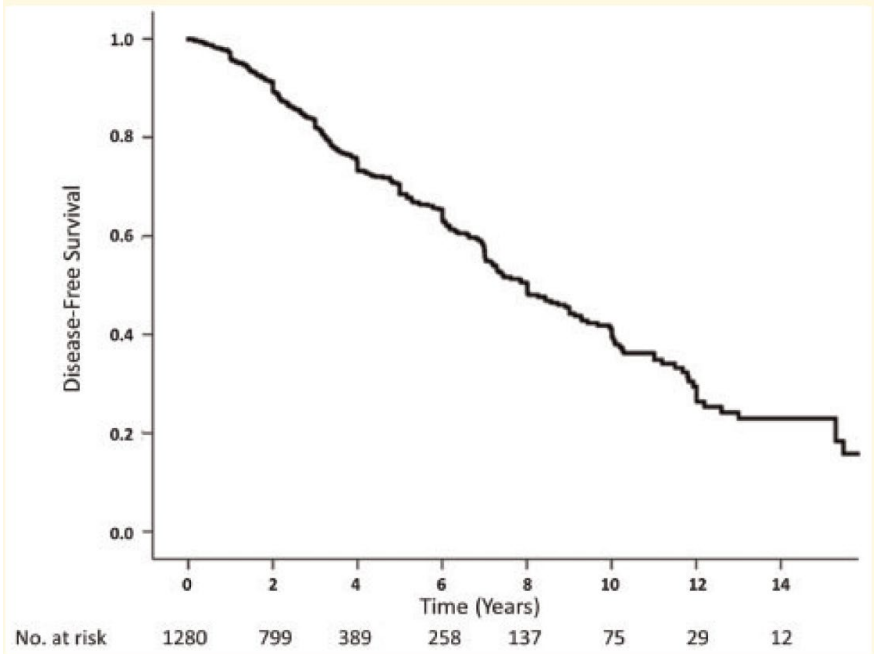


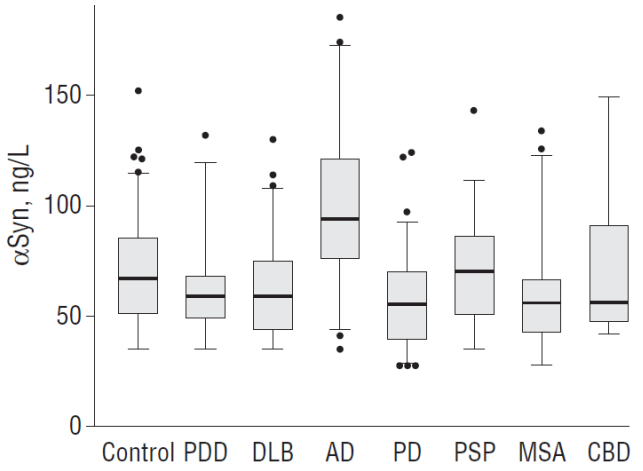
Figure 1 Kaplan-Meier plot of disease-free survival (i.e. free of parkinsonism or dementia) among patients with iRBD.

- **REM SBD** has conversion rate of ~6% annually to LBD.
  - Motor, cognitive, autonomic-increased risk for conversion.

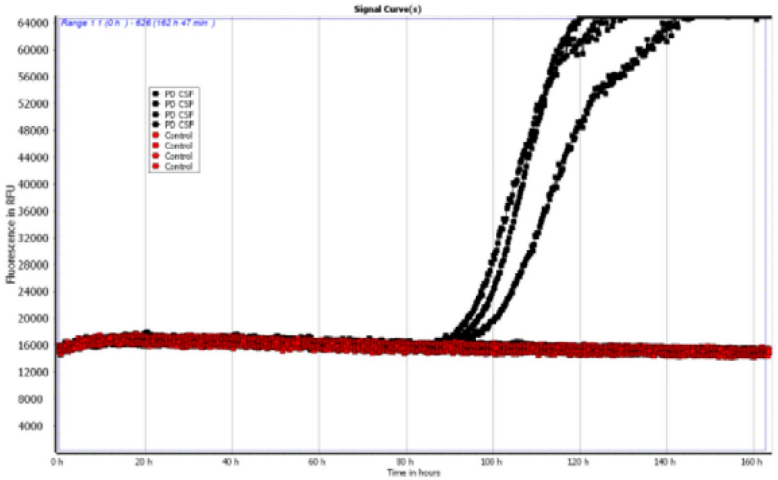
From Postuma et al, *Brain* 2019

CSF α-Synuclein

- CSF α-syn LBD<HC, AD[1,2]
  - Preanalytical factors (HgB)
- Newer Assays
  - Phospho/Oligo α-syn[3]
  - RT-QuIC (sens/spec>90%)[4-6]



From Hall et al *Arch Neurol* 2012

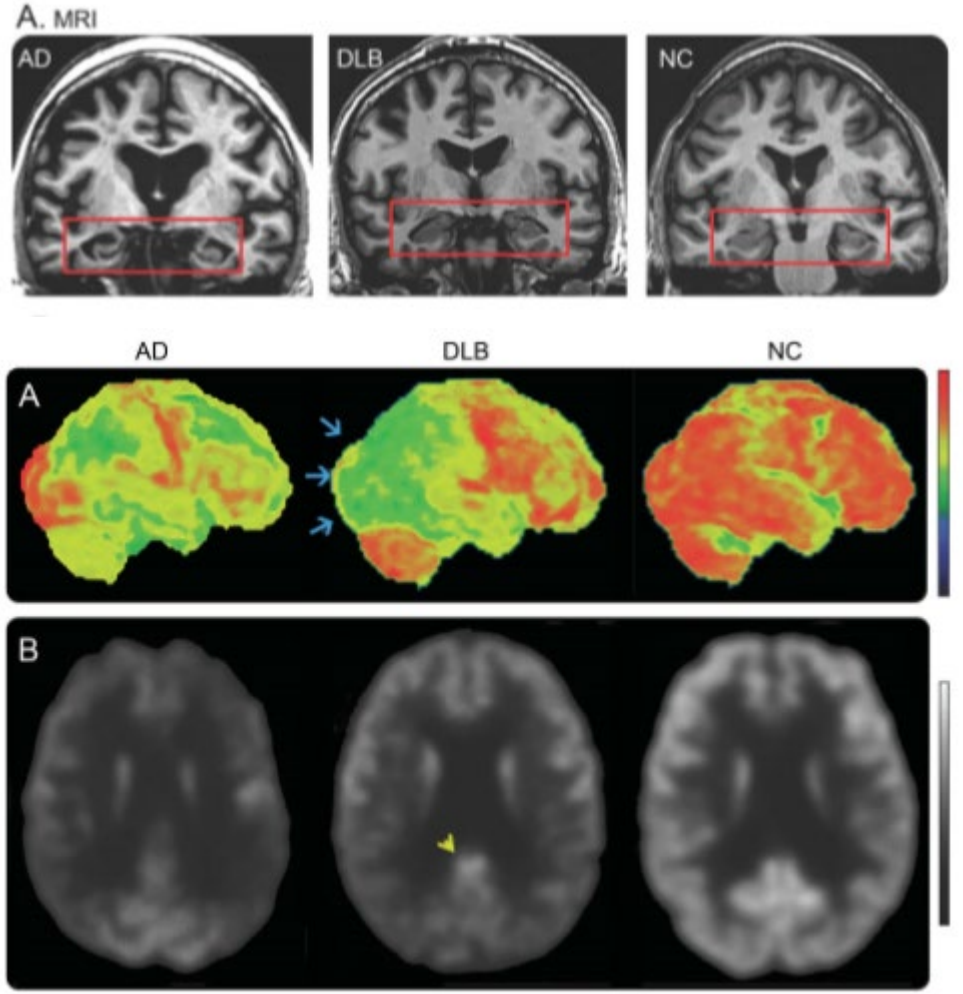


From Fairfoul et al *Ann Clin Trans Neurol* 2016

1. Mollenhauer et al Lancet Neurol 2011; 2. Kang et al, *JAMA Neurol* 2013; 3. Shi et al *Alz Dement 2018; 4*.Shahnawaz et al *JAMA Neurol* 2017; 5. Groveman et al *Acta Neuropathol* 2018; 6. van Rumund et al *Ann Neurol* 2019.

Supportive Biomarkers for DLB

- Relative preservation of MTL on structural MRI.
- Posterior occipital hypometabolism and cingulate island sign on FDG-PET.

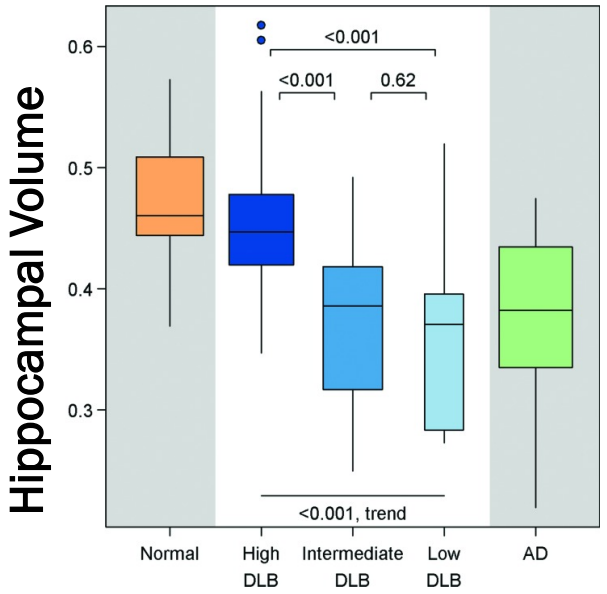


Adapted From McKeith et al Neurology 2017

AD co-pathology and LBD biomarkers

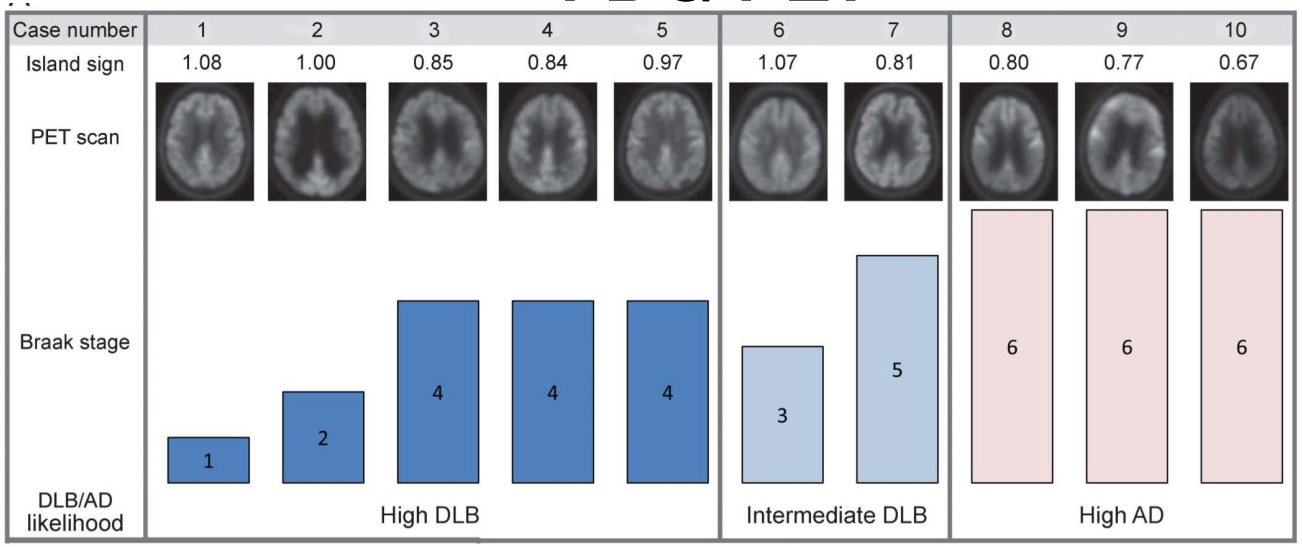
- AD co-pathology has a strong influence on structural and functional imaging markers in LBD.

Structural MRI



From: Kantarci et al Neurol. 2012

FDG-PET



From: Graff-Radford et al Neurol. 2014

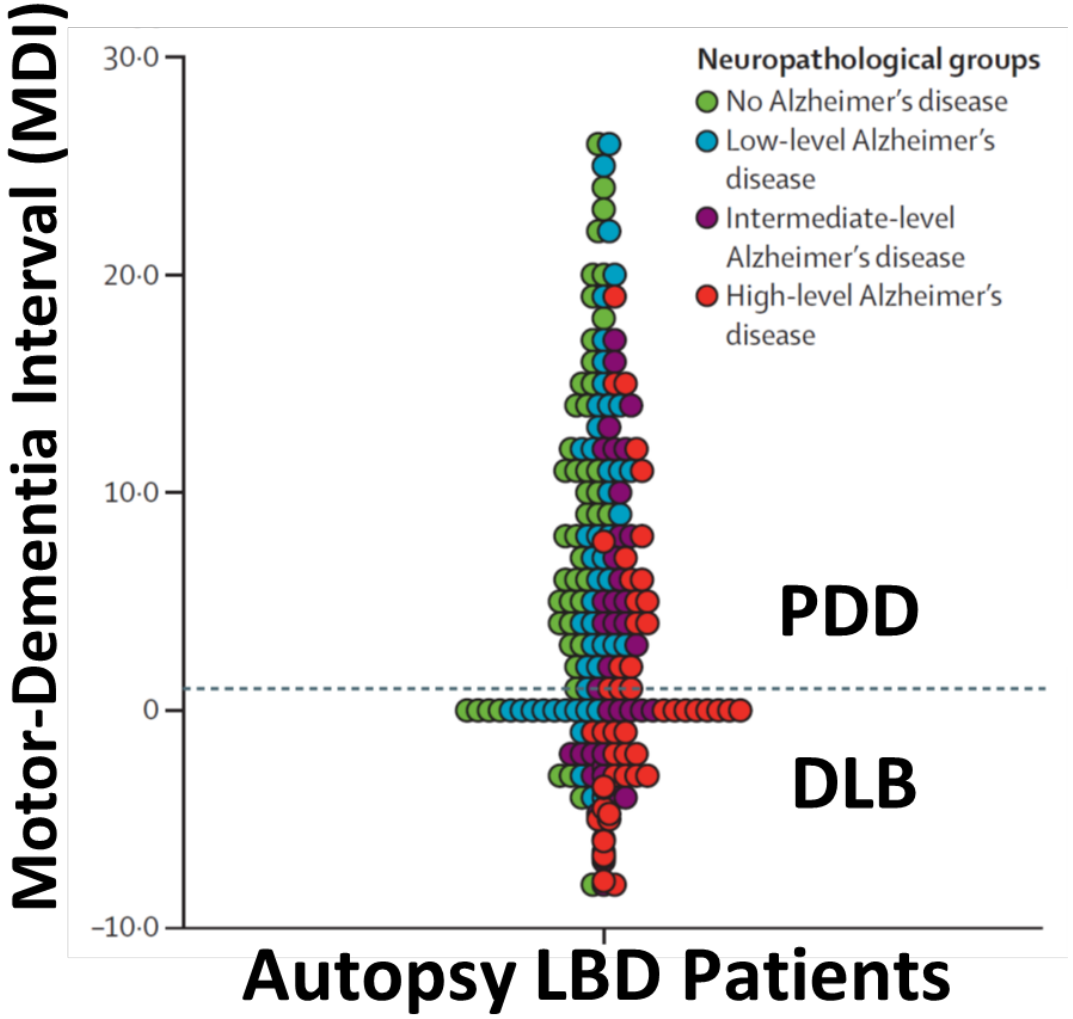
Overview

- Biomarkers for α-synucleinopathy

- Interpretation of AD biomarkers in LBD

AD co-pathology in LBD

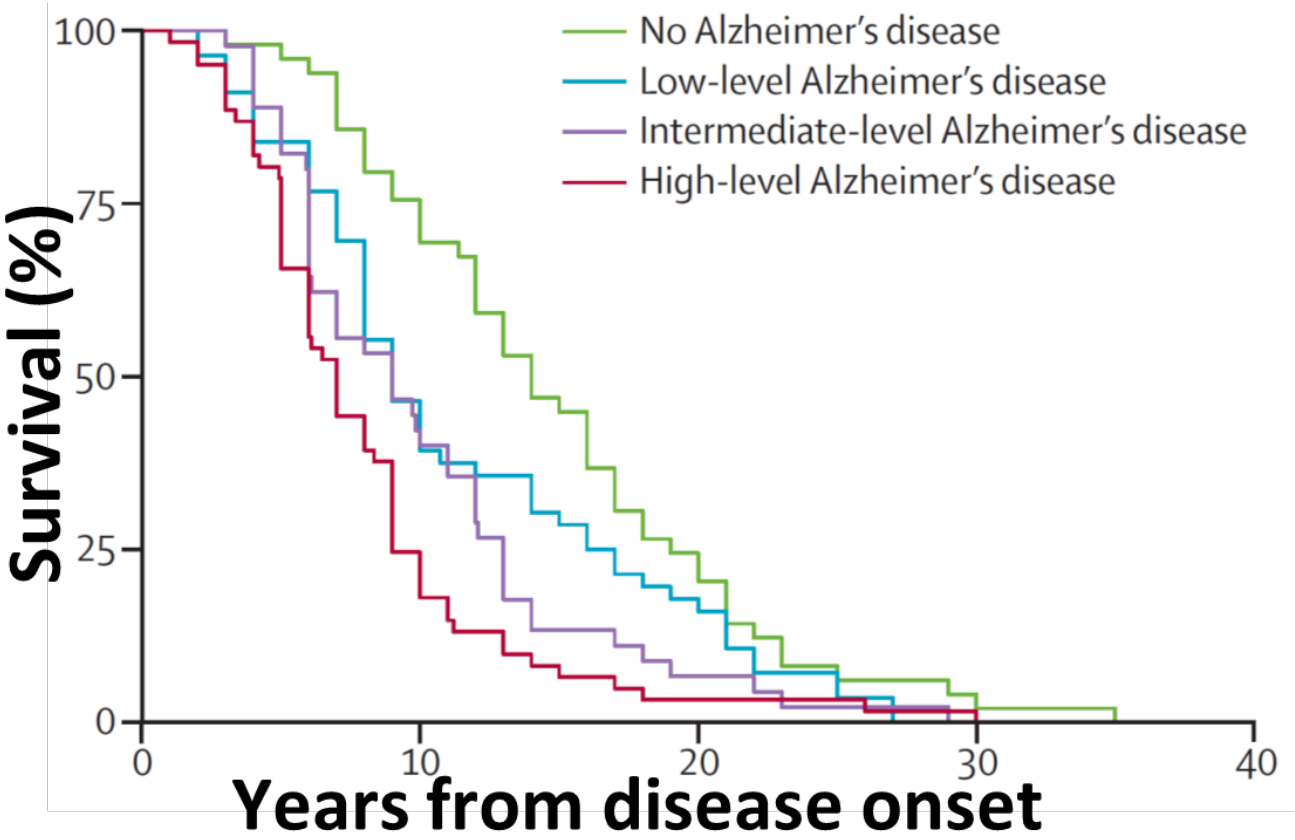
- **Multi-center cohort of autopsy-confirmed clinical LBD** (PDD=115 , DLB=98)
- **Clinically significant AD neuropathologic change is common in LBD (~50%)**
  - 40% PDD, 70% DLB
- **No neuropathologic or genetic substrate can reliably differentiate PDD vs DLB.**



From: Irwin et al. *Lancet Neurol*. 2017

AD co-pathology in LBD

- **AD co-pathology is associated with poor prognosis in LBD**
  - Shorter interval to dementia
  - Shorter overall survival
- **Specific cognitive and motor symptoms in LBD[1-4]**
  - Episodic memory, naming impairment
  - Less Hallucinations/Fluctuations
  - Postural instability



1. Peavey et al *Parkinsonism Relat Disord* 2016
2. Kraybill et al, *Neurology* 2005
3. Coughlin et al, *Ann Neurol* 2019
4. Selikhova et al, *Brain* 2009

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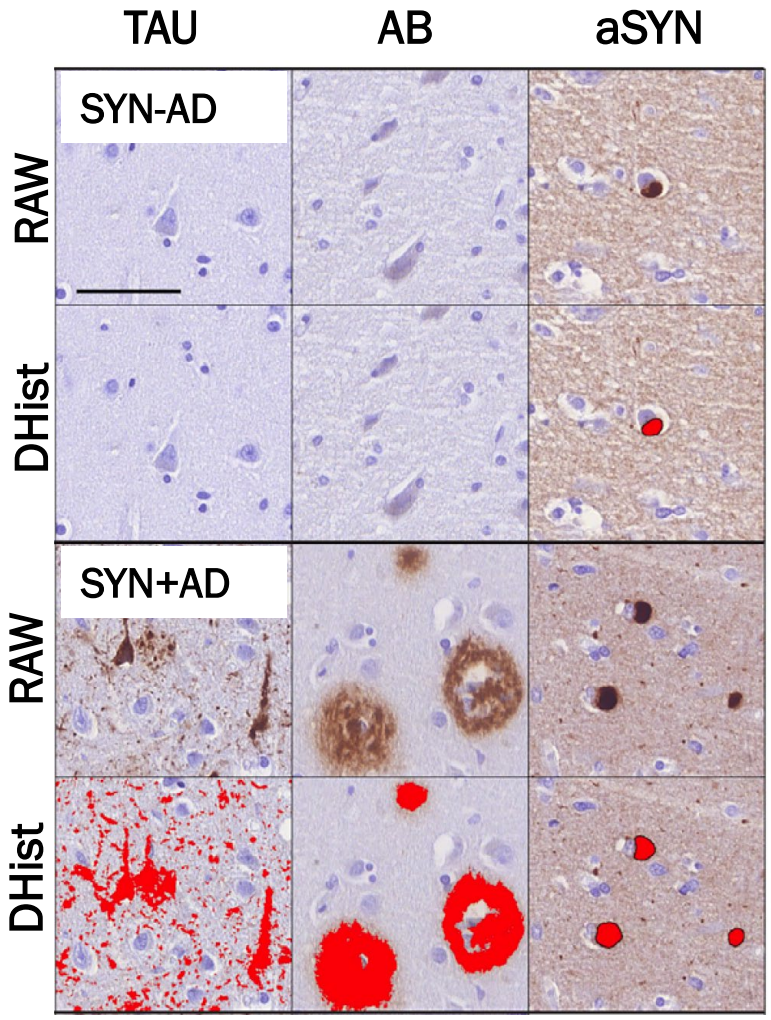
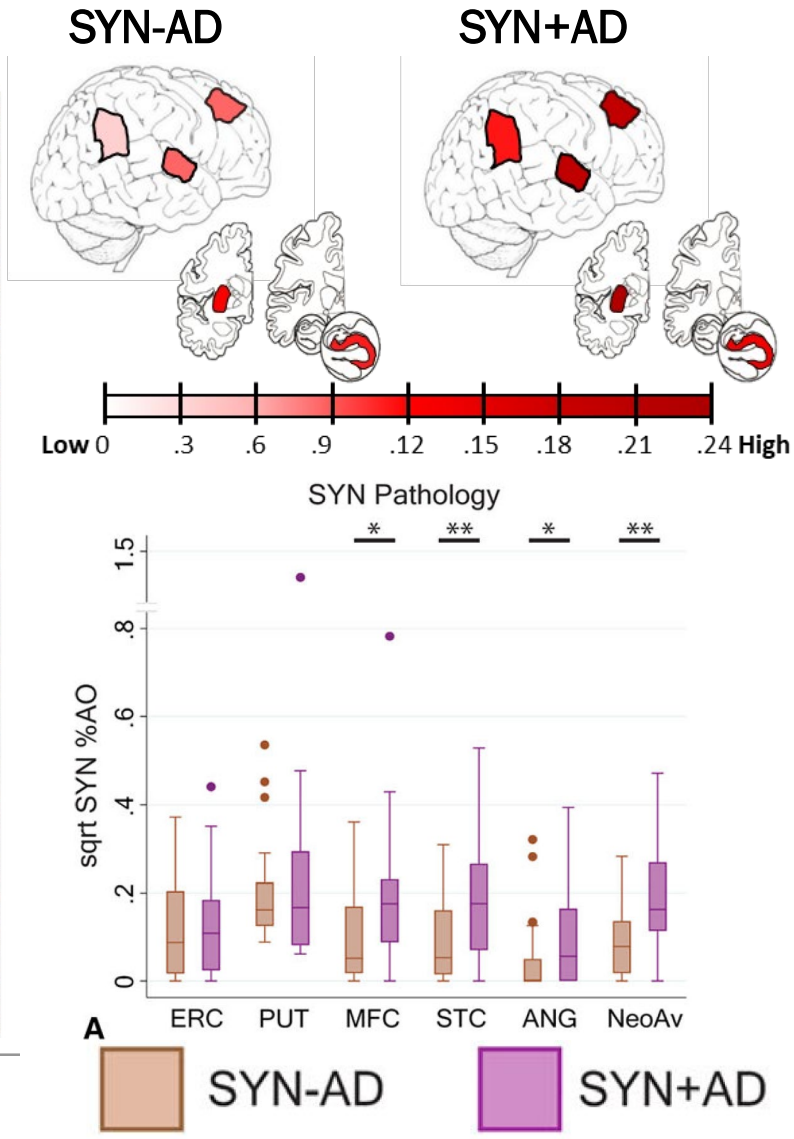
From: Irwin et al. *Lancet Neurol*. 2017

AD Co-pathology in LBD

- Digital Histopathology (SYN+AD=35, SYN-AD=20)
- AD co-pathology in LBD is associated with greater relative neocortical distribution of Lewy pathology.





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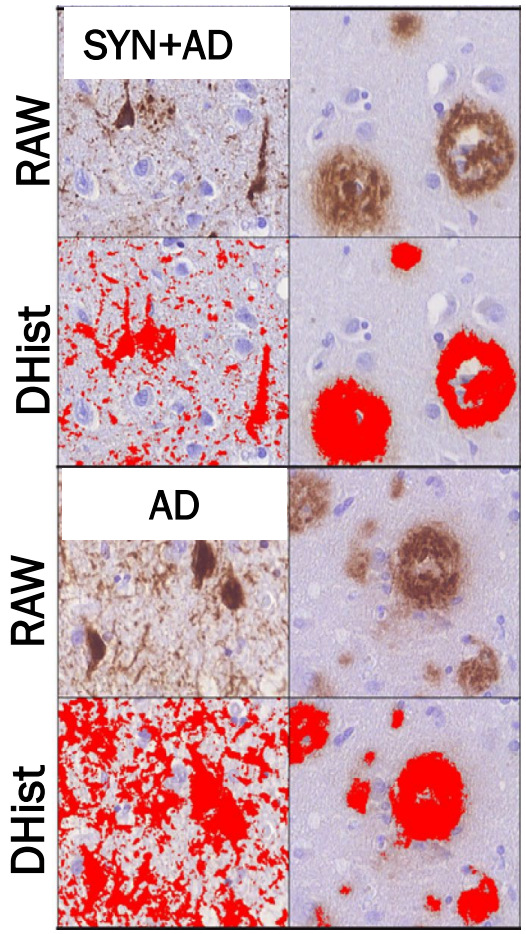
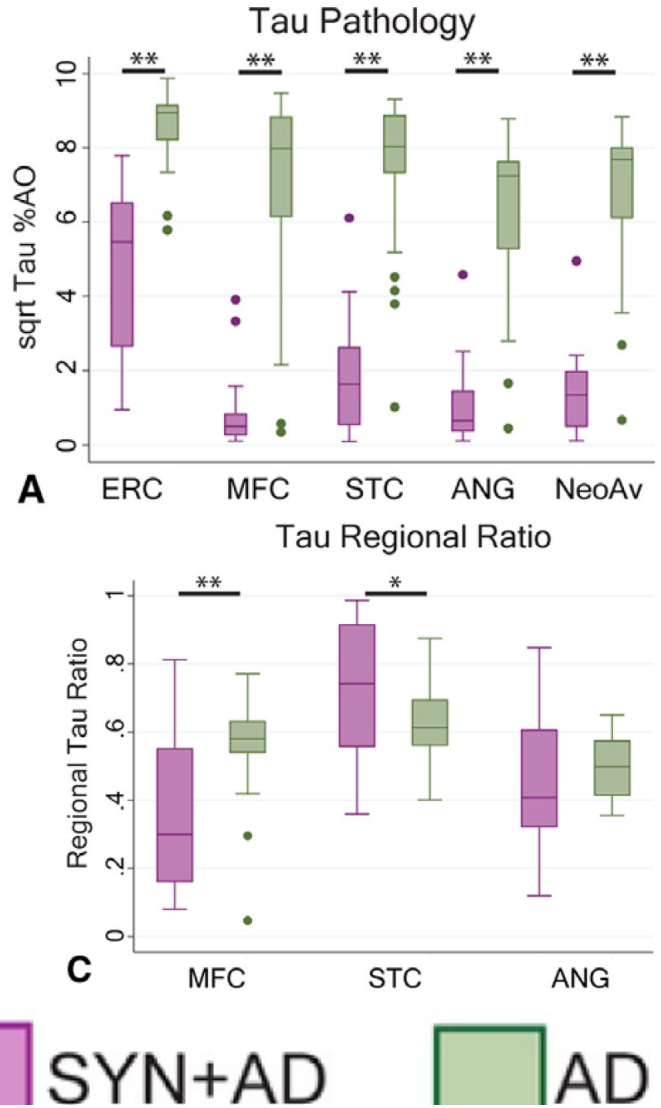
Coughlin et al, *Ann Neurol* 2018

AD Tau Co-pathology in LBD

- Digital Histopathology (SYN-AD=20, AD without SYN=20)
- Tau pathology in AD> LBD.
- LBD Tau had greater relative temporal distribution than AD.
- LBD tau correlated with cognition (r=-0.4-0.6, p<0.001).





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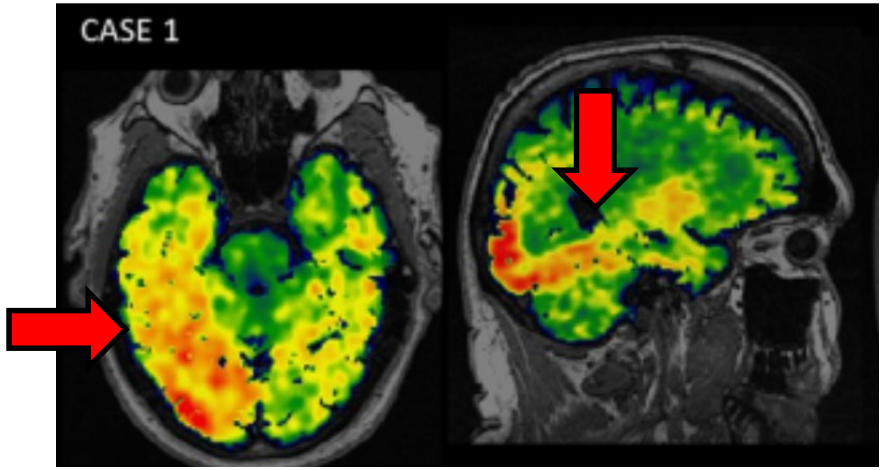
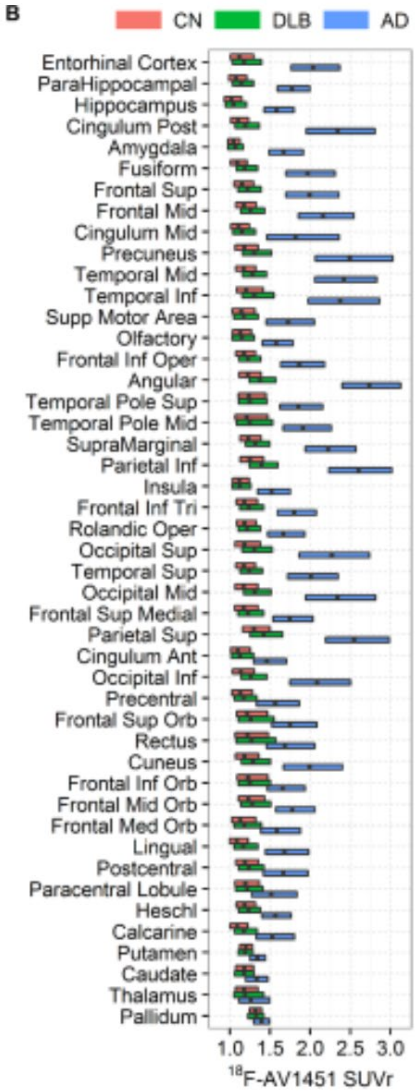
Coughlin et al, *Ann Neurol* 2018

AD Tau co-pathology in LBD *in vivo*

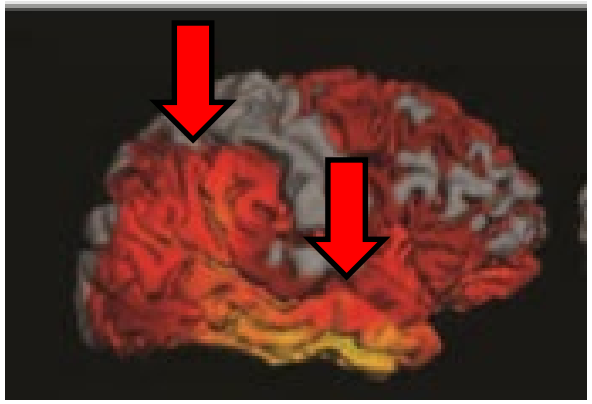
PET TAU AV-1451 DLB



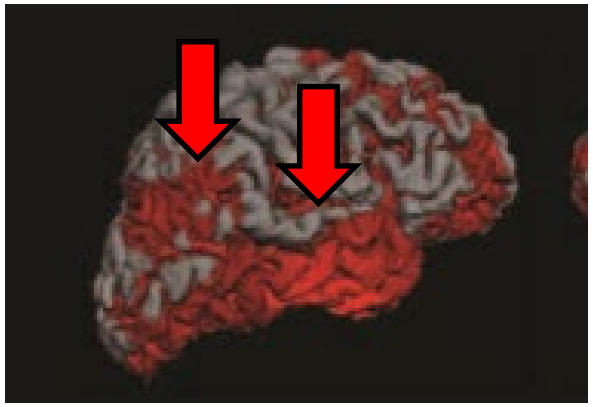
From Kantarci et al, *Annals Neurol* 2016



PET TAU AV-1451 DLB



PET TAU AV-1451 PDD



From Gomperts et al, *JAMA Neurol* 2016

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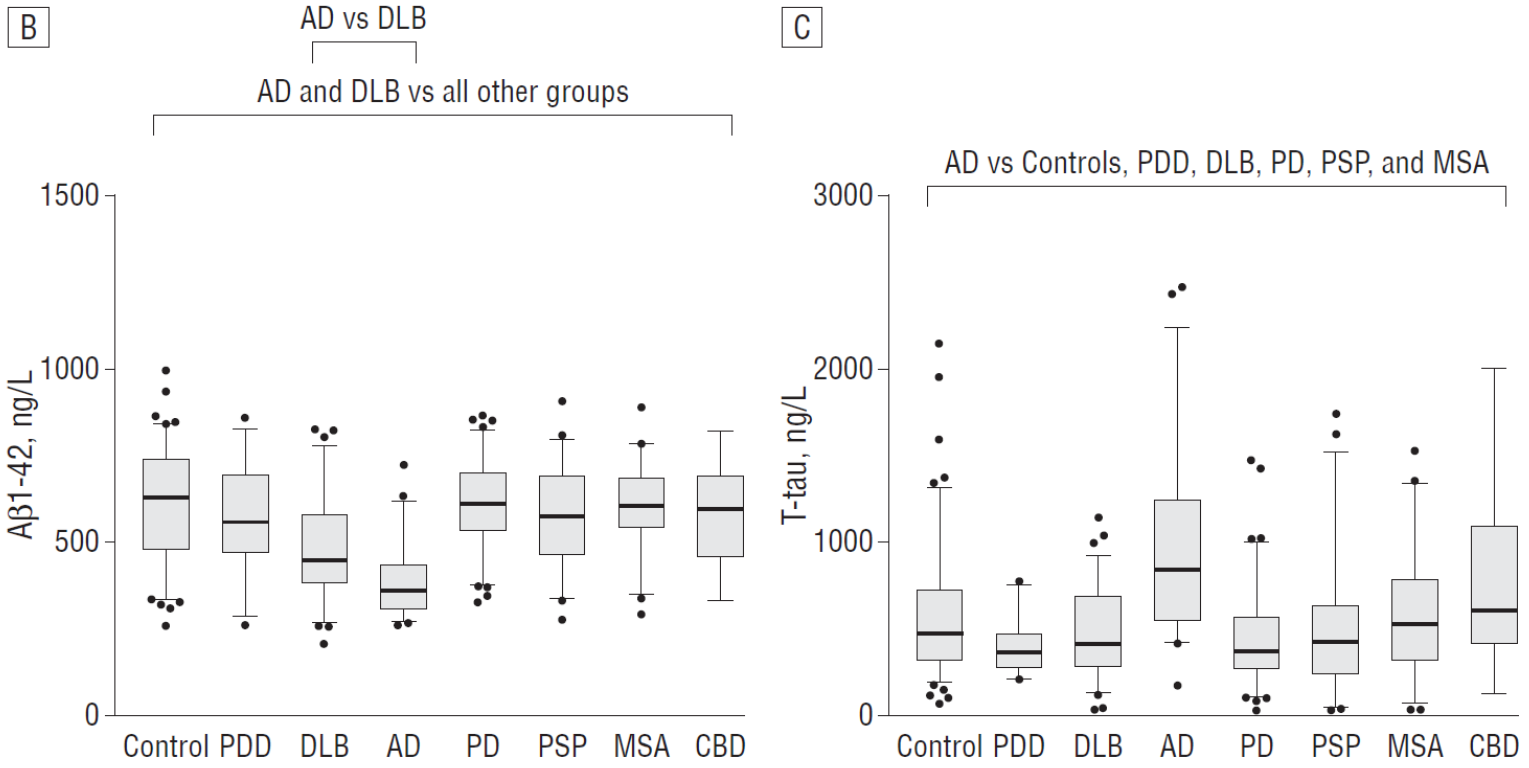
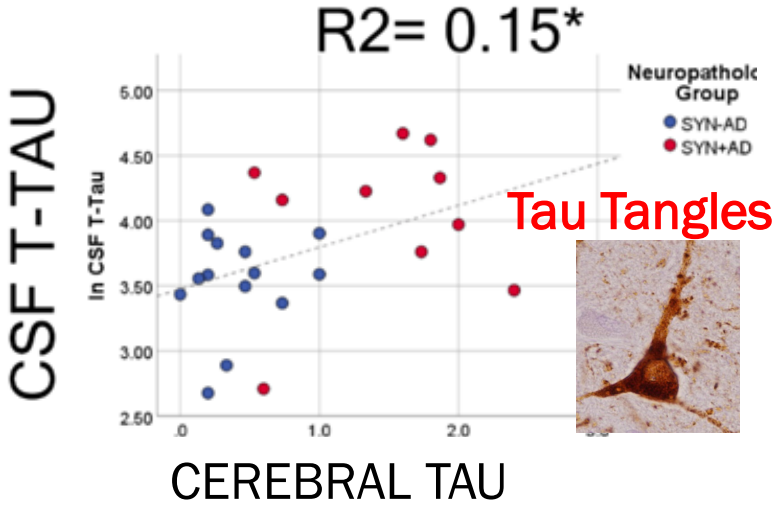
Detecting AD co-pathology in LBD *in vivo*

- AD CSF BM in LBD clinical cohorts reflect frequency of AD co-pathology in autopsy studies.



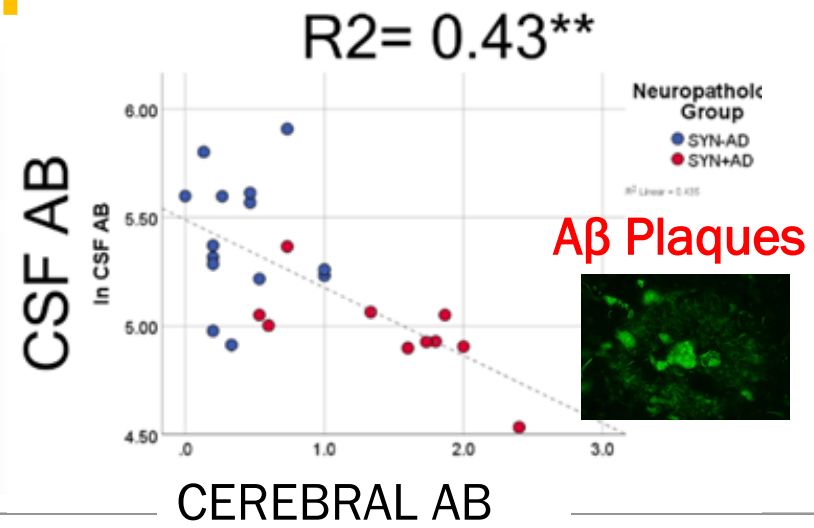
From Hall et al *Arch Neurol* 2012

Detecting AD co-pathology in LBD *in vivo*

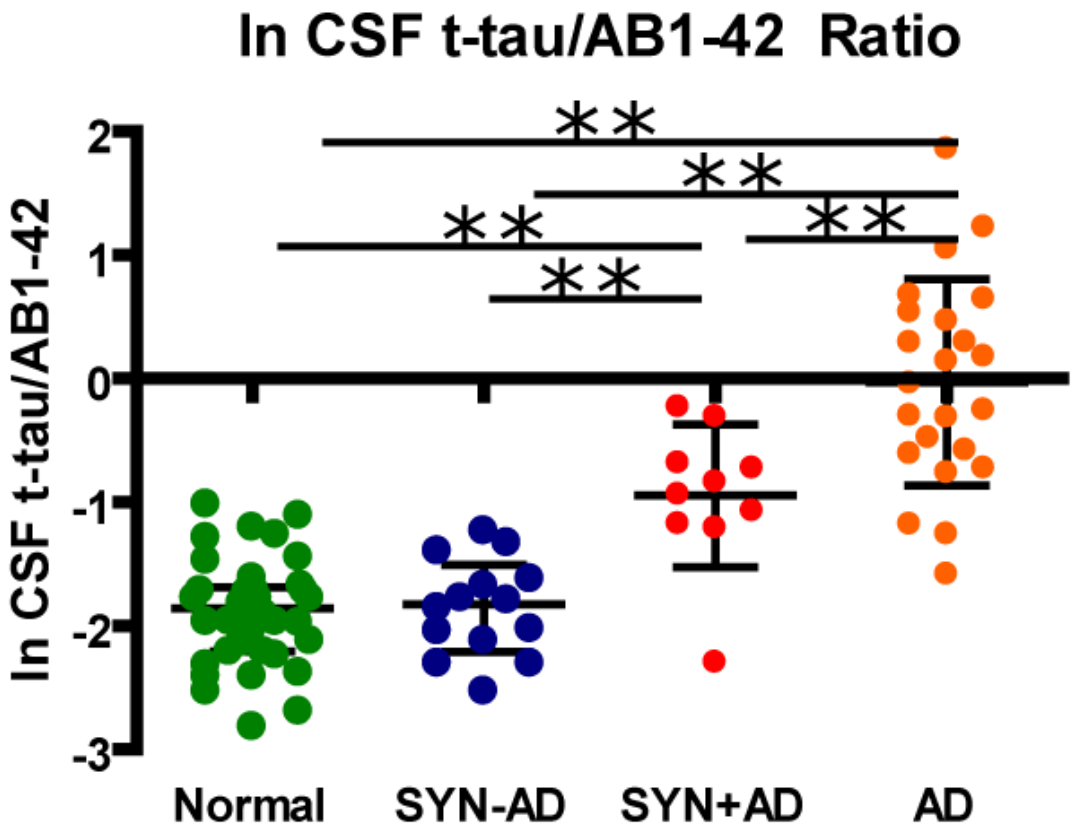


Tau Tangles

CSF

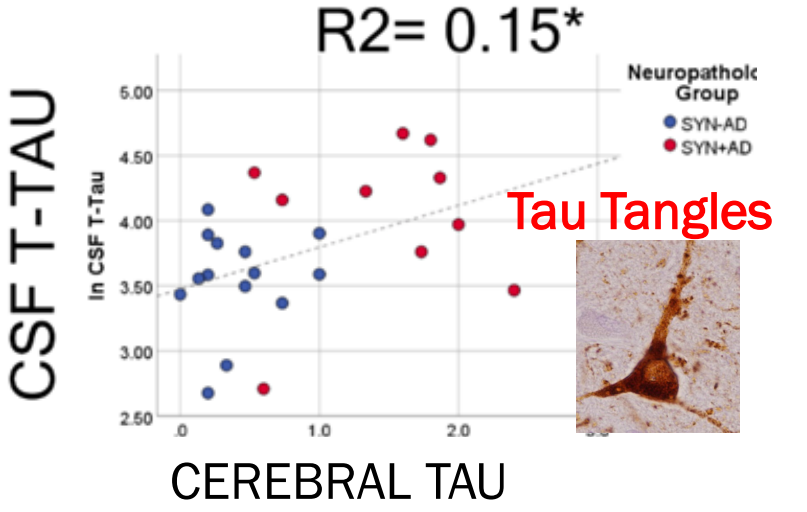


Aβ Plaques



From: Irwin et al, *Neurol* 2017

Detecting AD co-pathology in LBD *in vivo*



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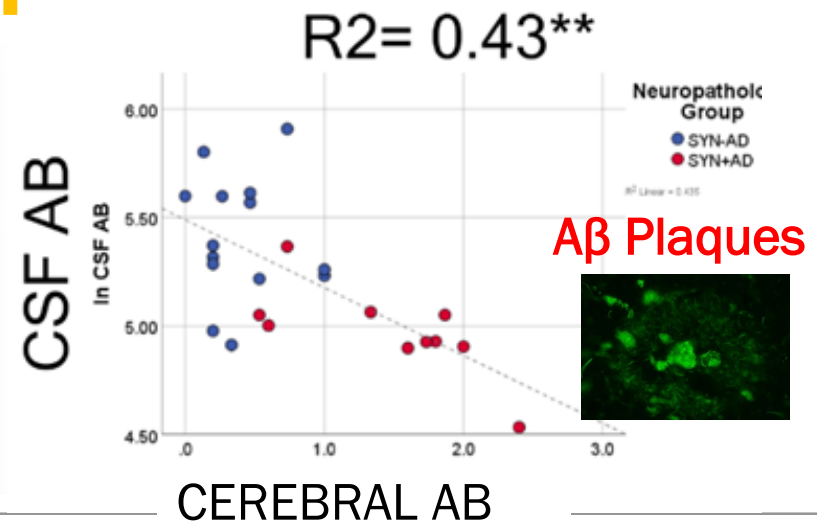

From: Irwin et al, *Neurol* 2017

CSF amyloid β 1-42 predicts cognitive decline in Parkinson disease

A. Siderowf, MD, MSCE
S.X. Xie, PhD
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J. Duda, MD
A. Chen-Plotkin, MD
L.M. Shaw, PhD
V. Van Deerlin, MD, PhD
J.Q. Trojanowski, MD, PhD
C. Clark, MD

Neurology® 2010;75:1055-1061

RESEARCH PAPER

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

A W Lemstra,[1] M H de Beer,[1,2] C E Teunissen,[3] C Schreuder,[4] P Scheltens,[1] W M van der Flier,[5] S A M Sikkes[6]

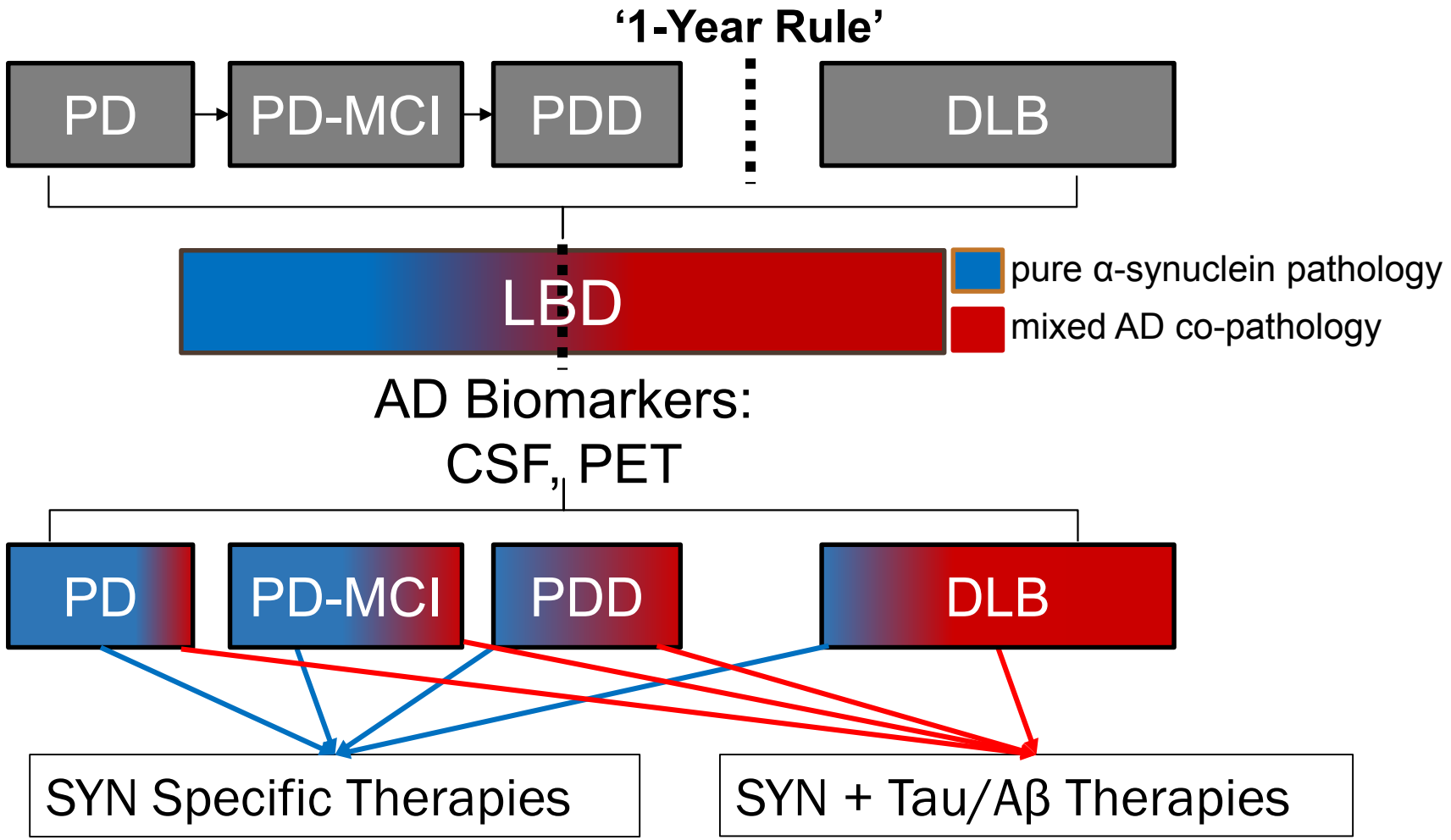
Lemstra AW, *et al*. *J Neurol Neurosurg Psychiatry* 2017;**88**:113–118. doi:10.1136/jnnp-2016-313775

SUMMARY- Biomarker Stratification of LBD

Classic Clinical Phenotypes (SYN Biomarkers)

AD Biomarker Stratified Phenotypes

Future Therapies/ Clinical trials



From: Coughlin, Hurtig and Irwin. *Movement DO*. 2019

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Jeffrey Kaye
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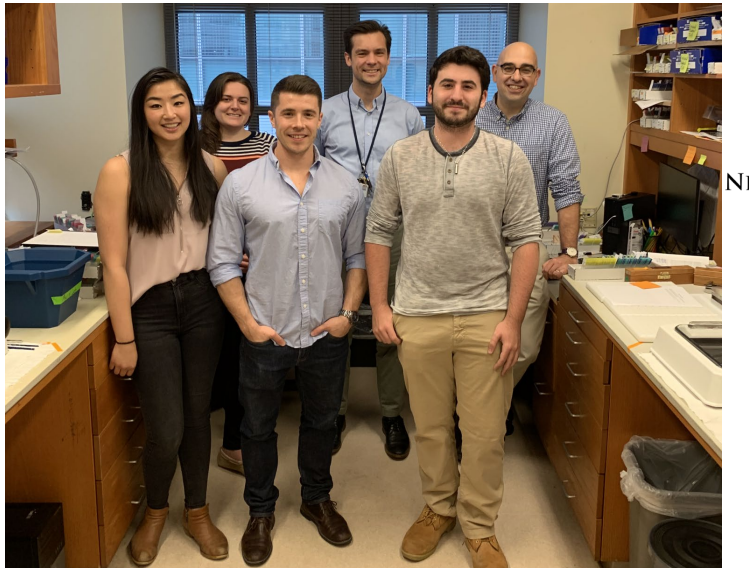
Joseph Quinn

Cleveland Clinic
James Leverenz



Patients and their families

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