

Dementia in Parkinson's disease and Dementia with Lewy Bodies - 9 things to know

Dr Rimona Weil

Consultant Neurologist and Wellcome Clinician Scientist
National Hospital for Neurology and Neurosurgery, Queen Square
Dementia Research Centre, UCL
16th November 2018

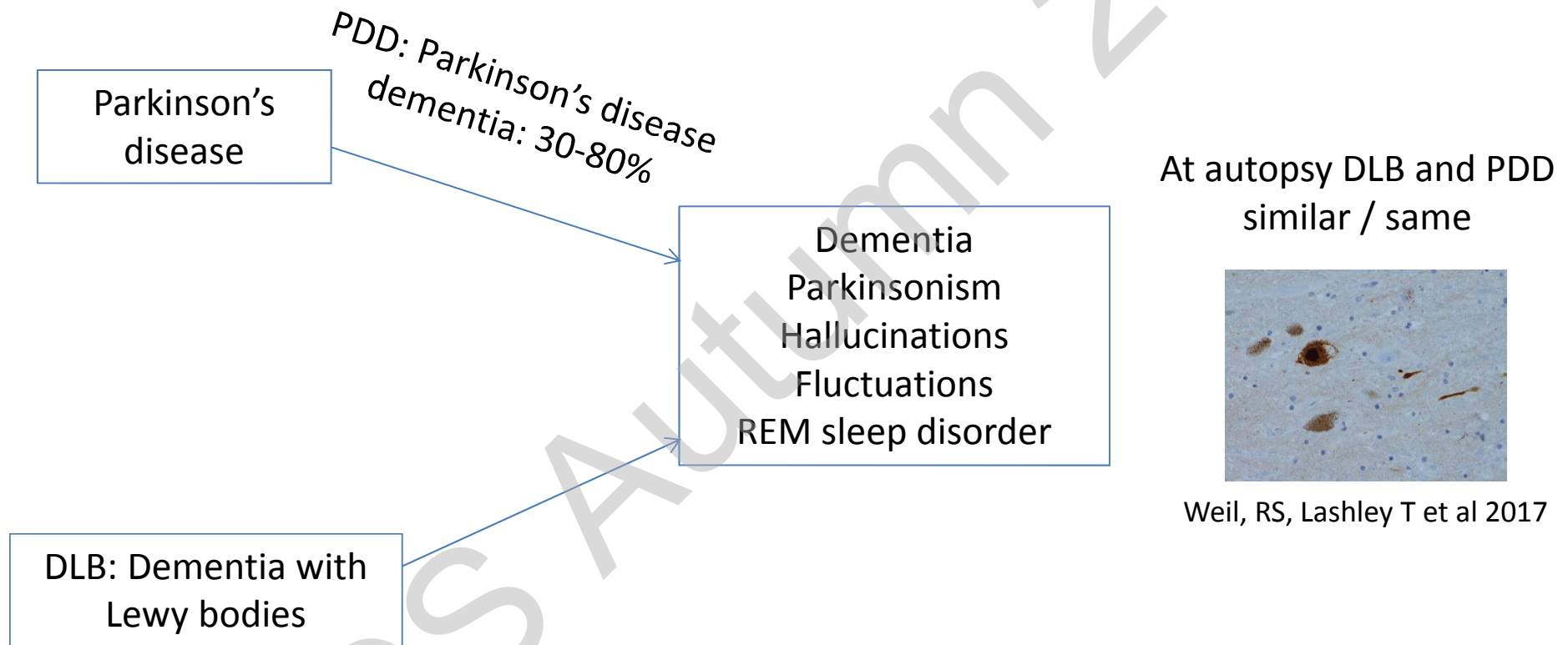
9 things to know about DLB/PDD

1. PDD and DLB have more in common than they differ
2. They are more common than you might think
3. Diagnostic criteria are changing
4. We are starting to gain insights into how visual hallucinations happen
5. REM sleep disorder is an important symptom before and during DLB
6. The type of dementia in DLB is different from Alzheimer's
7. Imaging can support diagnosis
8. It's not just about the Lewy Body
9. New treatments are looking promising

1. DLB and PDD have more common than they differ

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Parkinson's dementia and Dementia with Lewy Bodies



Currently defined by the timing of when dementia versus Parkinsonism happen
The One Year Rule

Problems with the one year rule

- A lot depends on who is making the diagnosis
- It's a continuum
- Cognitive changes are seen in prodromal Parkinson's disease -
- And increase the risk of Parkinson's developing (Darweesh 2017)

Movement Disorders Official Journal of the International Parkinson and Movement Disorder Society

VIEWPOINT

Abolishing the 1-Year Rule: How Much Evidence Will Be Enough?

Ronald B. Postuma, MD, MSc,^{1*} Daniela Berg, MD,^{2*} Matthew Stern, MD,³ Werner Poewe, MD,⁴ C. Warren Olanow, MD, FRCPC,⁵ Wolfgang Oertel, MD,⁶ Kenneth Marek, MD,⁷ Irene Litvan, MD,⁸ Anthony E. Lang, OC, MD, FRCPC,⁹ Glenda Halliday, PhD,¹⁰ Christopher G. Goetz, MD,¹¹ Thomas Gasser, MD,² Bruno Dubois, MD, PhD,¹² Piu Chan, MD, PhD,¹³ Bastiaan R. Bloem, MD, PhD,¹⁴ Charles H. Adler, MD, PhD,¹⁵ and Günther Deuschl, MD¹⁶

¹Department of Neurology, Montreal General Hospital, Montreal, Quebec, Canada
²Department of Neurodegeneration, Hertie-Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases, Tuebingen, Germany

Research

JAMA Neurology | **Original Investigation**

Association Between Poor Cognitive Functioning and Risk of Incident Parkinsonism

The Rotterdam Study

Sirwan K. L. Darweesh, MD, MSc; Frank J. Wolters, MD, MSc; Ronald B. Postuma, MD, MSc; Bruno H. Stricker, MB, PhD; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; M. Kamran Ikram, MD, PhD; M. Arfan Ikram, MD, PhD

IMPORTANCE Cognitive dysfunction is a common feature among patients with parkinsonism, including Parkinson disease (PD). However, there is a scarcity of data on cognitive functioning before parkinsonism diagnosis, a stage at which patients may still respond to putative disease-modifying interventions.

← Editorial
+ Supplemental content

2. DLB and PDD are more common than you might think

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2. DLB and PDD are more common than you might think

DLB

- 2nd commonest cause of dementia
 - Around 20% of all dementia
 - 10-30% of dementia at post mortem (1 in 7)
 - Often not recognised in life – diagnosed as Alzheimer's or Vascular dementia
-
- **Parkinson's dementia**
 - Affects 50% of Parkinson's after 10 years – but a lot of variability
 - Higher rates with older age at diagnosis

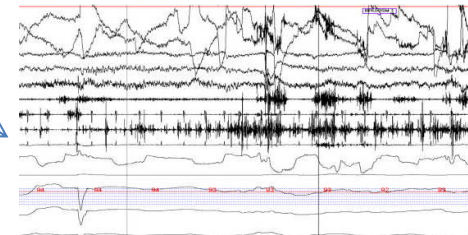
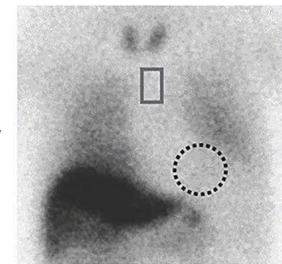
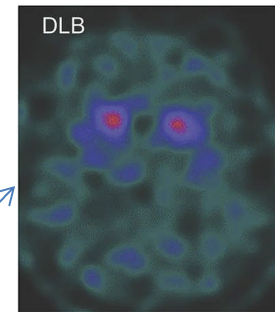
3. Diagnostic criteria are changing

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DLB: Revised criteria

McKeith et al Neurology 2017

- Essential features
 - Progressive cognitive decline interfering with daily life
 - Prominent memory impairment evident with progression
 - Attention, executive, visuo-perceptual may occur early
- Core clinical
 - Fluctuating cognition
 - Recurrent visual hallucinations
 - REM sleep disorder
 - Parkinsonism: tremor / rigidity / parkinsonism
- Indicative biomarkers
 - Reduced uptake DaT uptake (PET or SPECT)
 - Low uptake on Iodine MIBG myocardial scintigraphy
 - REM sleep without atonia on polysomnography
 - You can't use biomarkers alone



Supportive clinical features

- Severe sensitivity to antipsychotics
- Repeated falls and syncope
- Transient unexplained loss of consciousness
- Severe autonomic dysfunction – constipation, urine incontinence
- Hyposmia
- Non-visual hallucinations, Delusions
- Anxiety and depression

Supportive biomarkers

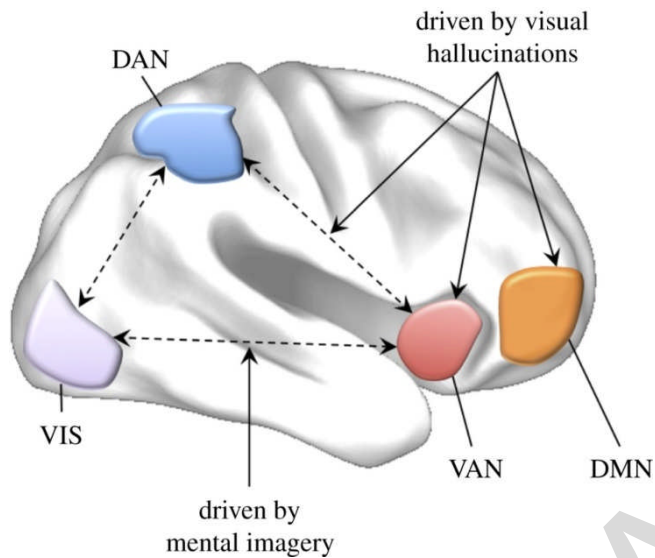
- Preserved medial temporal lobe
- General low uptake on CT perfusion
- Reduced PET occipital uptake
- Prominent slow on EEG with temporal sharp waves

4. We are starting to gain insights into how visual hallucinations happen

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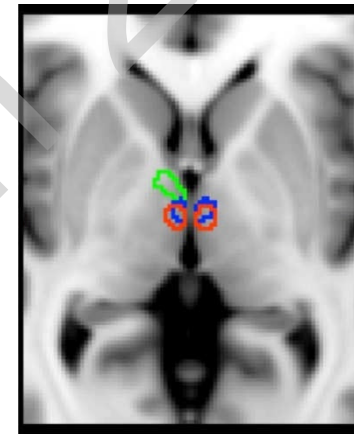
4. We are starting to gain insights into how visual hallucinations happen

Network changes



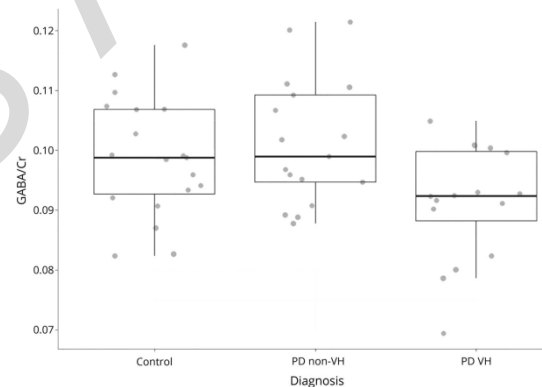
Shine 2015 Proc Royal Soc B

Thalamus



Onofrj Neuropsych dis & Treatment 2017
Erskine D, Mov Disord 2018

Occipital GABA



Firbank Neurology 2018

And
Serotonin...

5. REM sleep disorder is an important symptom before and during DLB

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SAS

My Jekyll and Hyde husband: Wife tells of lecturer's sleep disorder that makes him lash out at her in his dreams

By [TOM KELLY FOR THE DAILY MAIL](#)

PUBLISHED: 23:33, 1 July 2012 | **UPDATED:** 07:48, 2 July 2012



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By day he is a mild-mannered college lecturer and loving husband. By night he unwittingly transforms into a foul-mouthed wife beater.

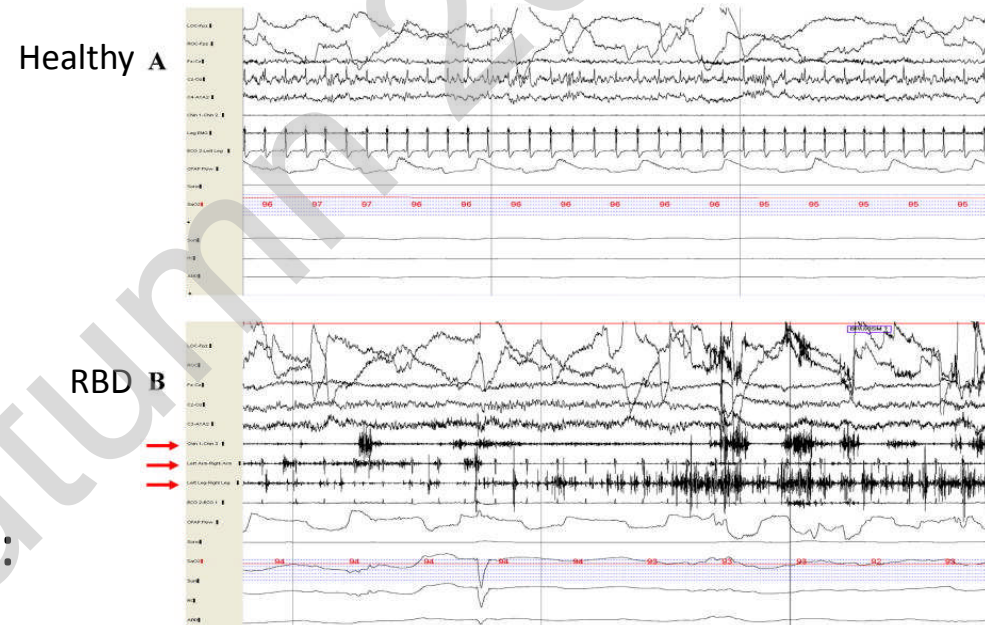
[Site](#) [Web](#)

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GREAT VALUE FA
24H MONEY BACK

REM Sleep disorder: RBD

- Strongly associated
- >90% with RBD will develop PD or DLB (or MSA) after 10 year follow-up
- And seen in autopsy-confirmed DLB
- May reflect distinct subtype: earlier disease onset, more rapid progression.

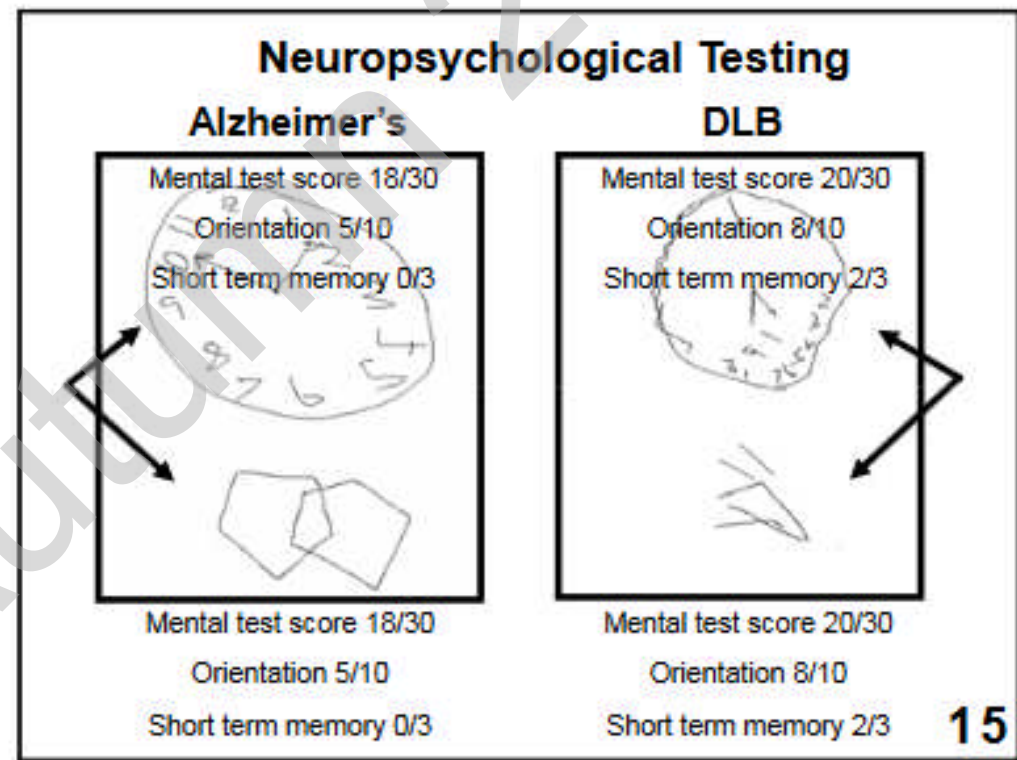


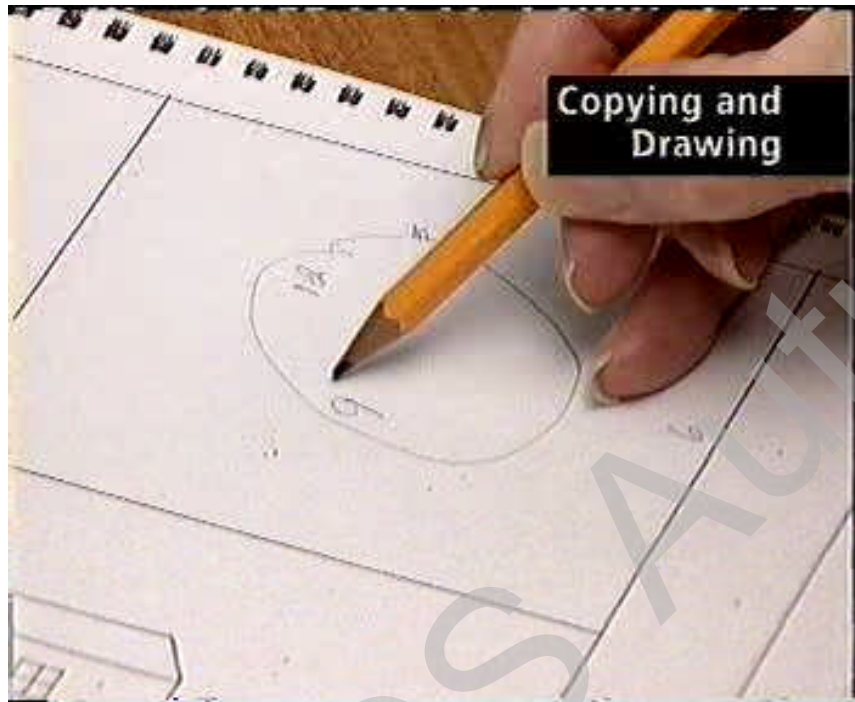
Arrows indicate chin and leg leads

6. The type of dementia differs from Alzheimer's

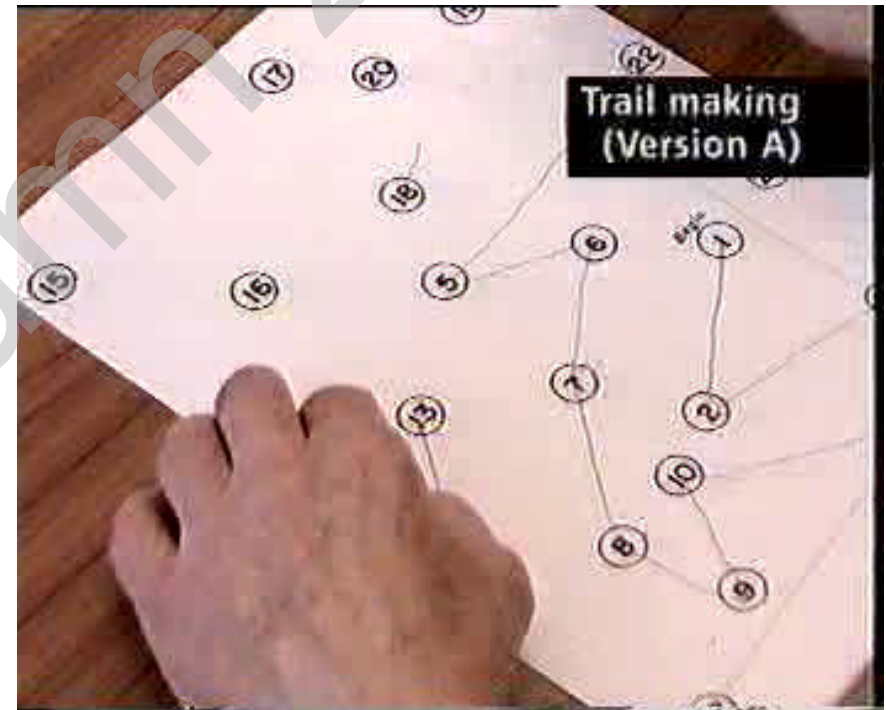
Neuropsychology profile

- Prominent visuo-perceptual dysfunction
- Problems with attention
- Memory better preserved





Clock drawing

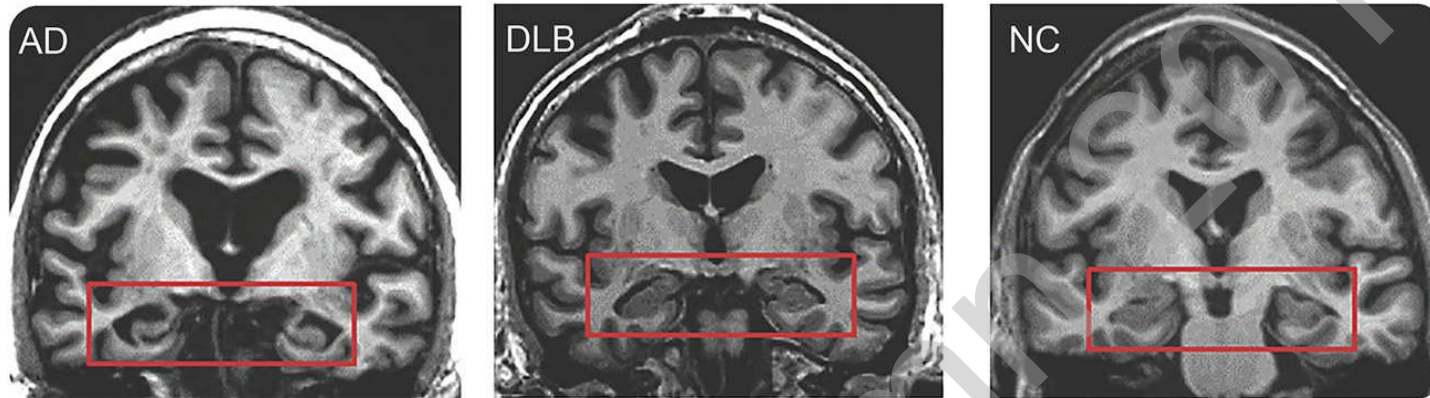


Trail making

7. Imaging can support diagnosis

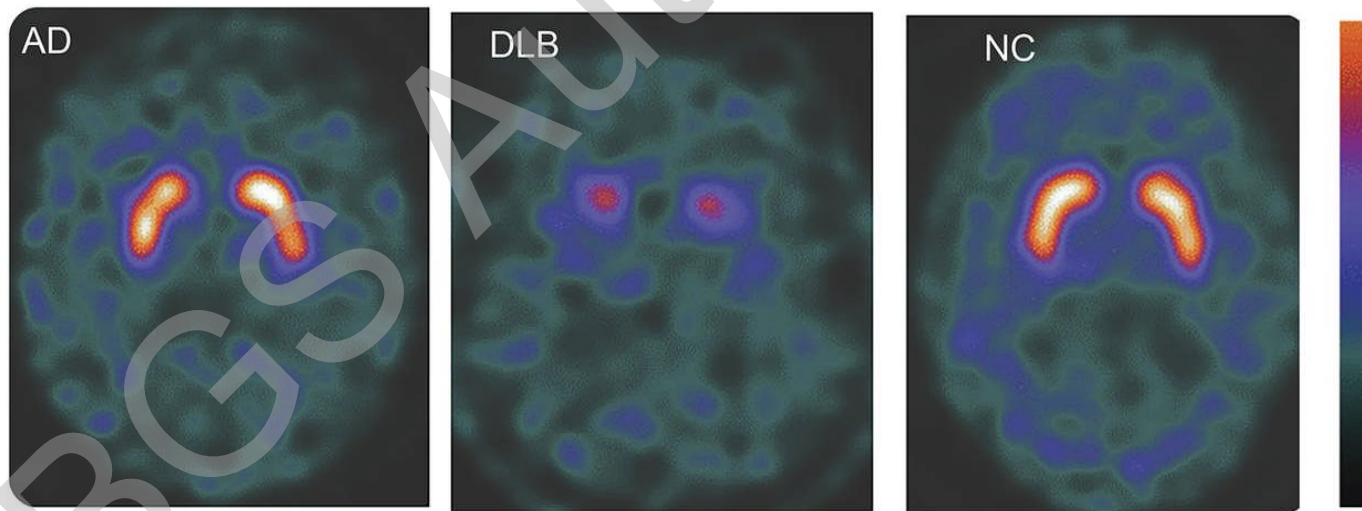
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MRI changes

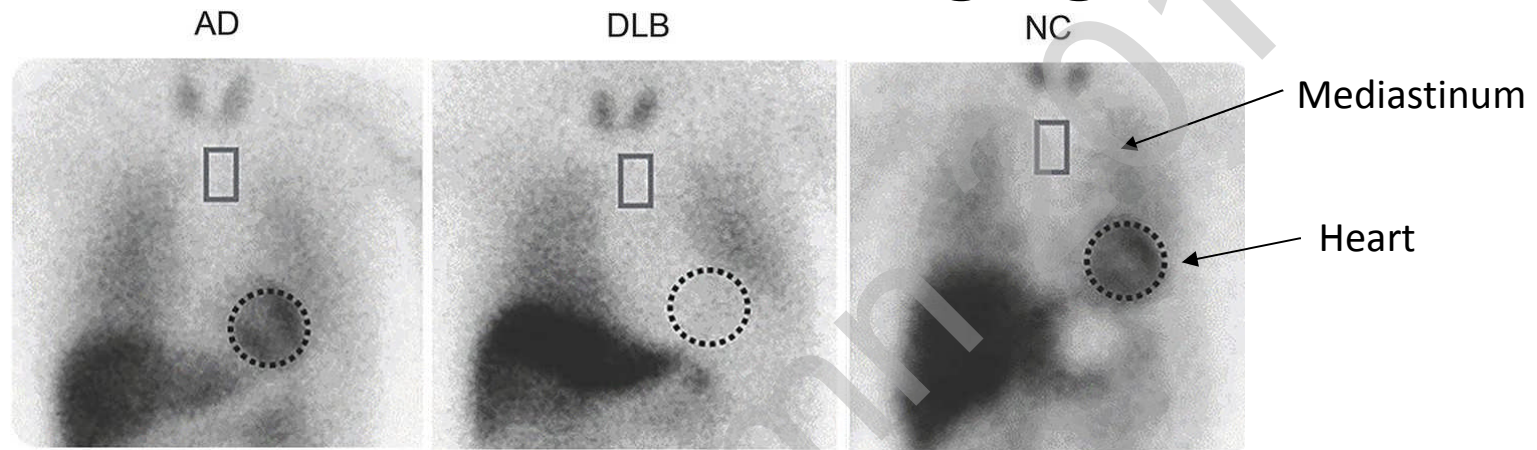


Also volume loss in parietal and frontal regions

FP-CIT SPECT



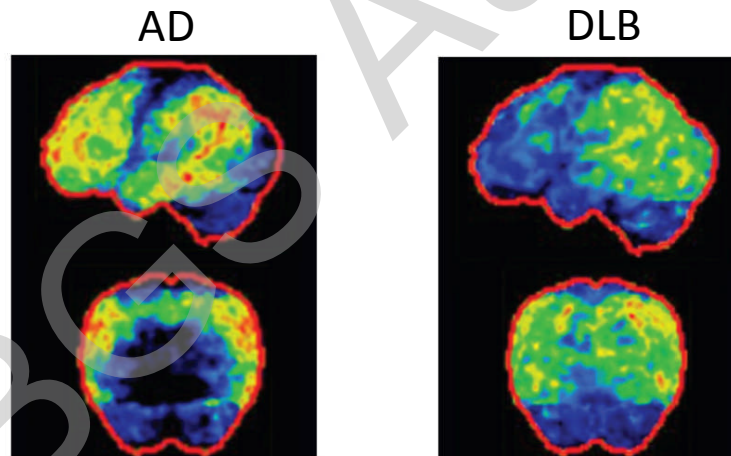
Cardiac MIBG imaging



Heart: Mediastinum ratio

McKeith, Neurology 2017

FDG-PET



Occipital hypometabolism
seen in DLB

Walker, Lancet 2015

8. It's not just about the Lewy Body

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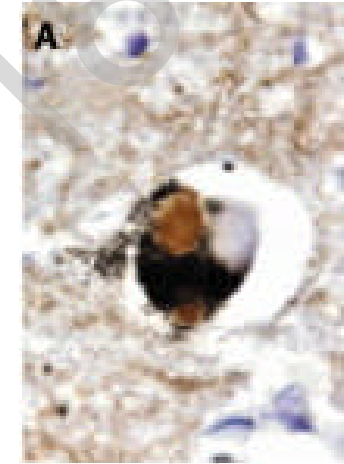


Lewy 1934, immigration file
National Archives Philadelphia

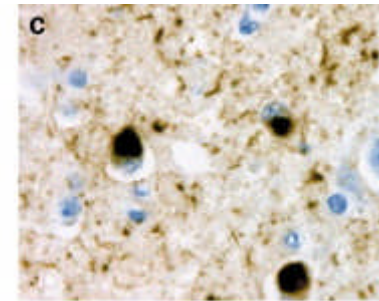
Pathology in DLB

- Hallmark: α -synuclein inclusions: Lewy bodies and Lewy neurites
- ?neuroprotective or toxic
- Cortical, limbic and brainstem
- No pathological difference between DLB and PDD

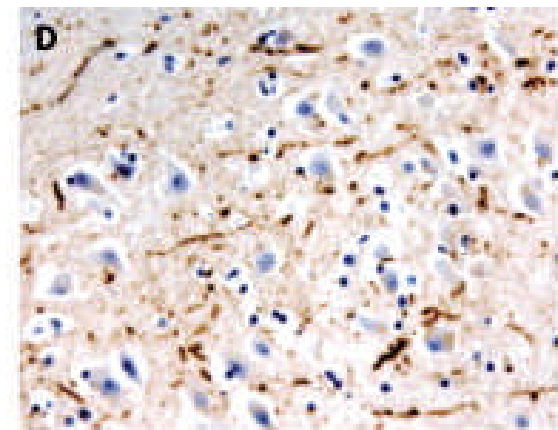
Lewy body in
brainstem



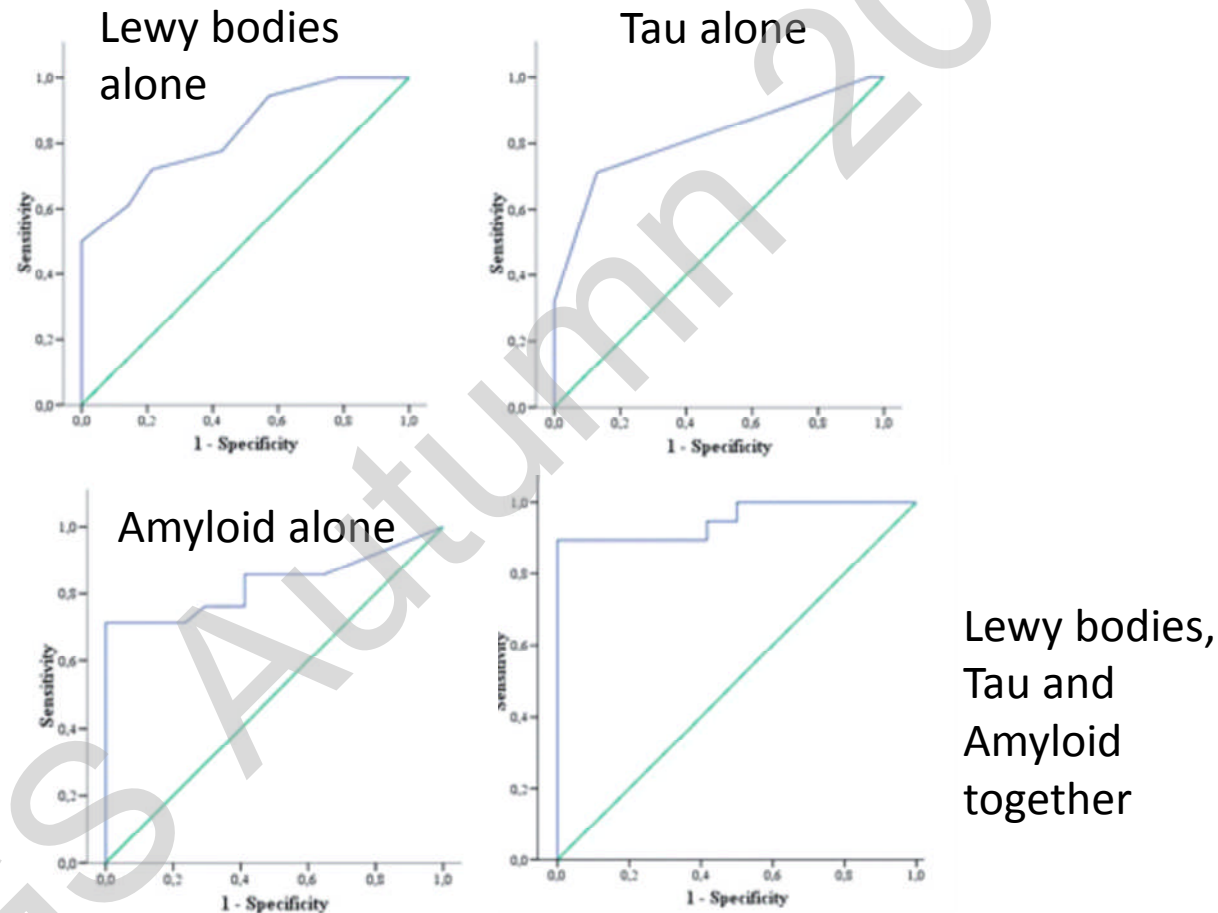
Lewy body in
cortex



Lewy neurite in
hippocampus



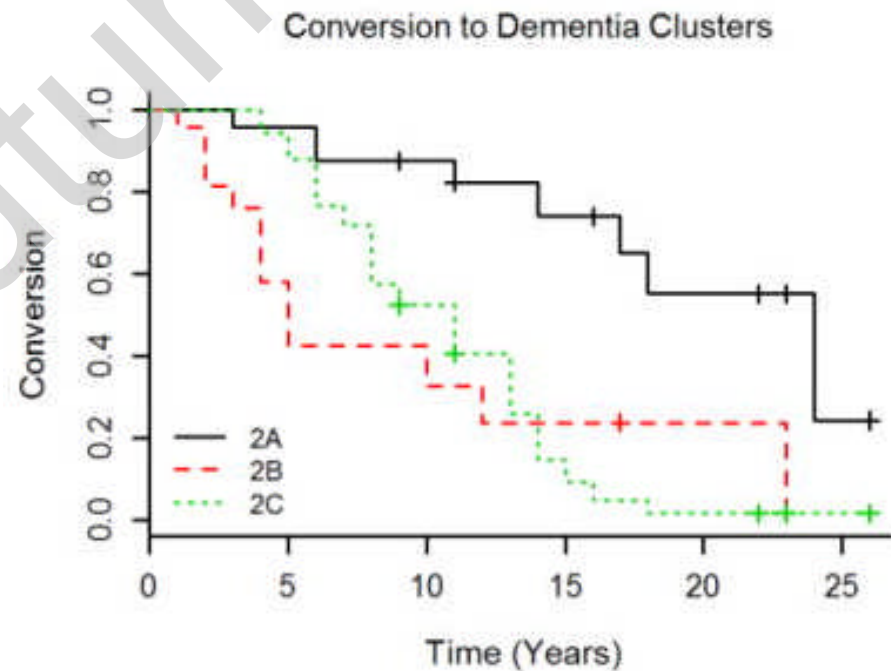
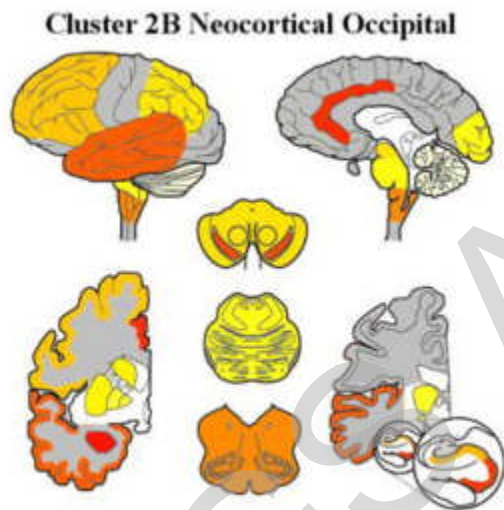
Synergy with other pathology



Combination of tau and amyloid with synuclein most linked with dementia

Distribution pattern may be important

Occipital Lewy pathology linked with more rapid dementia



9. New treatments for visual hallucinations are emerging

Managing hallucinations

- Stop or lower drugs that are worsening cognition
- Cholinesterase inhibitors can help
- Only treat if distressing
- Quetiapine NICE first line, but little evidence
- Best evidence for Clozapine - but causes agranulocytosis so must be prescribed within a clozapine service



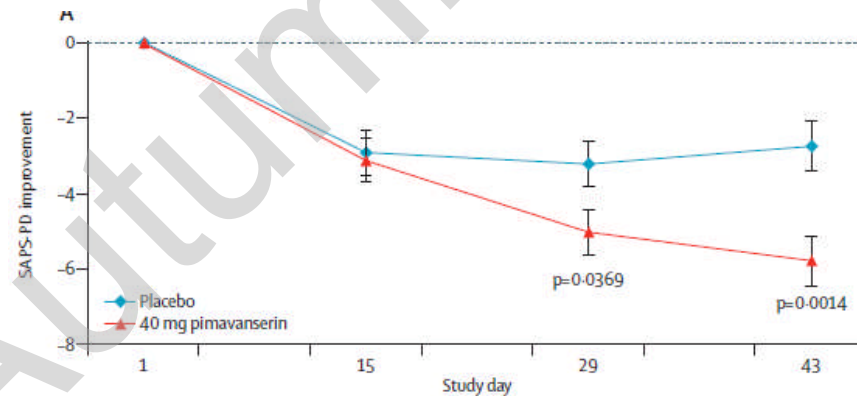
Pimavanserin for Visual Hallucinations

- 5HT_{2A} inverse agonist
- Improvement in hallucination score n=199

Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial



Jeffrey Cummings, Stuart Isaacson, Roger Mills, Hilde Williams, Kathy Chi-Burris, Anne Corbett, Rohit Dhall, Clive Ballard



But is it safe?

- Reports of double number of deaths in Pimavanserin arm
- 2/105 vs 1/94
- Prompted FDA investigation
 - Benefits outweigh risks
 - Patients with PDD/DLB have higher rate mortality
 - No new safety risks
 - Note: QT prolongation – caution with other QT lengthening drugs
 - Will continue to monitor

The image shows two screenshots. The top screenshot is a CNN news article titled "FDA worried drug was risky; now reports of deaths spark concern". The article is dated April 9, 2018, and is by Blake Ellis and Melanie Hicken. The bottom screenshot is the FDA website, specifically the "Drugs" section under "Drug Safety and Availability". The website header includes the U.S. Department of Health and Human Services and the U.S. Food & Drug Administration logo. The main content area features a sidebar with links to "Drug Alerts and Statements", "Medication Guides", "Drug Safety Communications", and "Drug Shortages". The main article on the page is titled "FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis". The article includes social media sharing options for Facebook, Twitter, LinkedIn, Pinterest, Email, and Print.

Reports of death spark concern

https://edition.cnn.com/2018/04/09/health/parkinsons-drug-nuplazid-invs/index.html

Health • FDA worried drug was risky; now reports of deaths spark concern

International Edition

FDA worried drug was risky; now reports of deaths spark concern

By Blake Ellis and Melanie Hicken, CNN Investigates

Updated 1000 GMT (1800 HKT) April 9, 2018

U.S. Department of Health and Human Services

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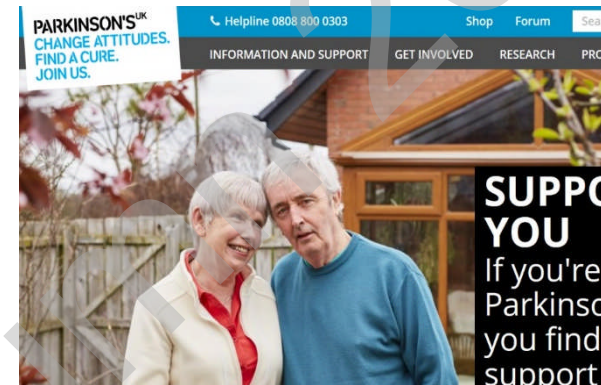
FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis

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There is support for this challenging disease



<https://www.lewybody.org/>



<https://www.parkinsons.org.uk>



Summary

- DLB/PDD is a common condition
- Clinical diagnosis – now can be supported by neuroimaging
- New treatments are becoming available
- Patients and carers benefit from support groups

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