Parkinson's disease Dementia and Lewy-Body Dementia

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Outline

A Lewy body dementia definition

B Diagnosis of Lewy body dementia

C What is LBD patient's journey?

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Lewy body dementia definition

PART A

What is Lewy body dementia?

Lewy

Body

Dementia

Neurodegenerative disorder

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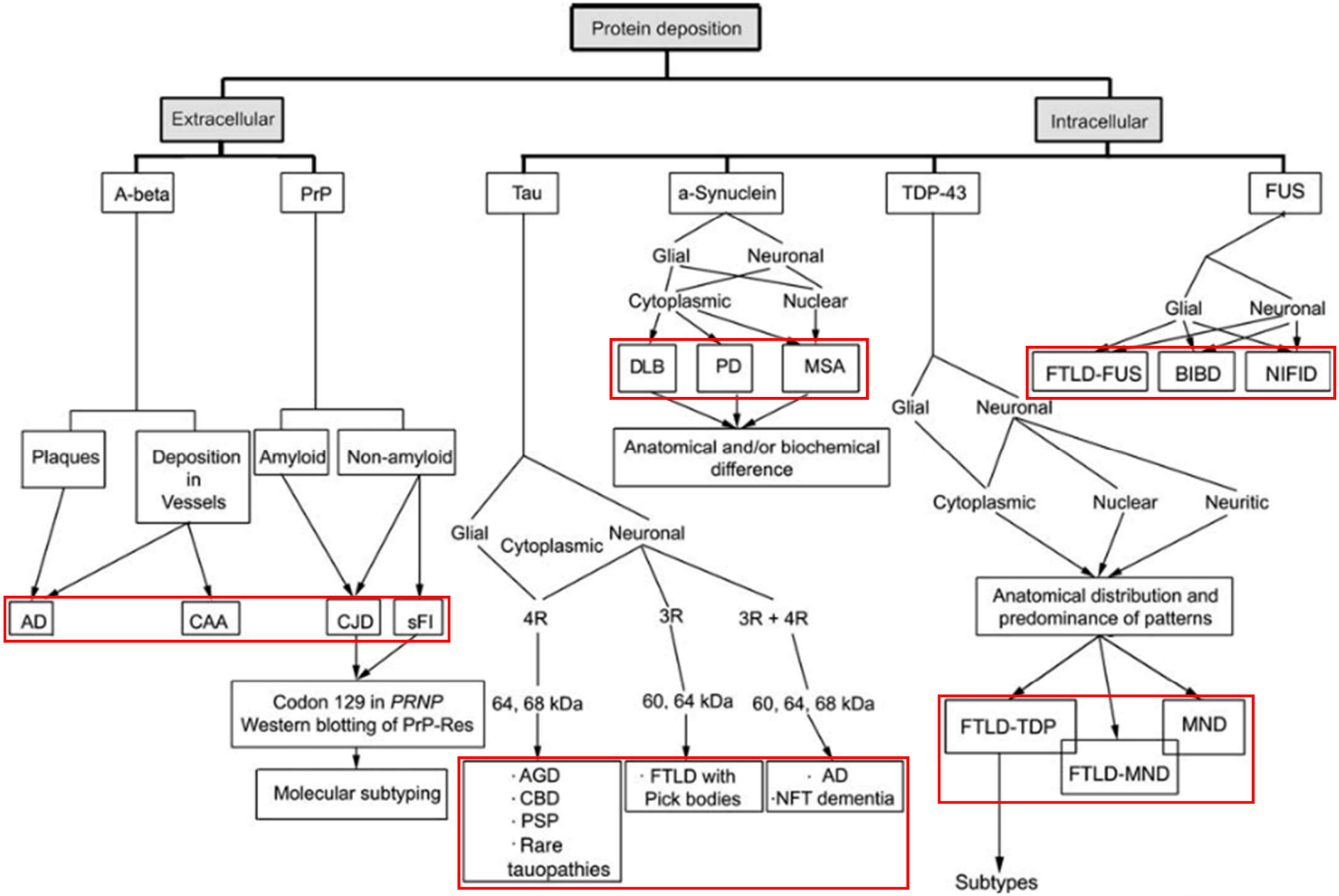

Kovacs GG et al. *Acta Neuropathol*. 2010

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What is Lewy body dementia?

Lewy

Body

Dementia

Neurodegenerative disorder

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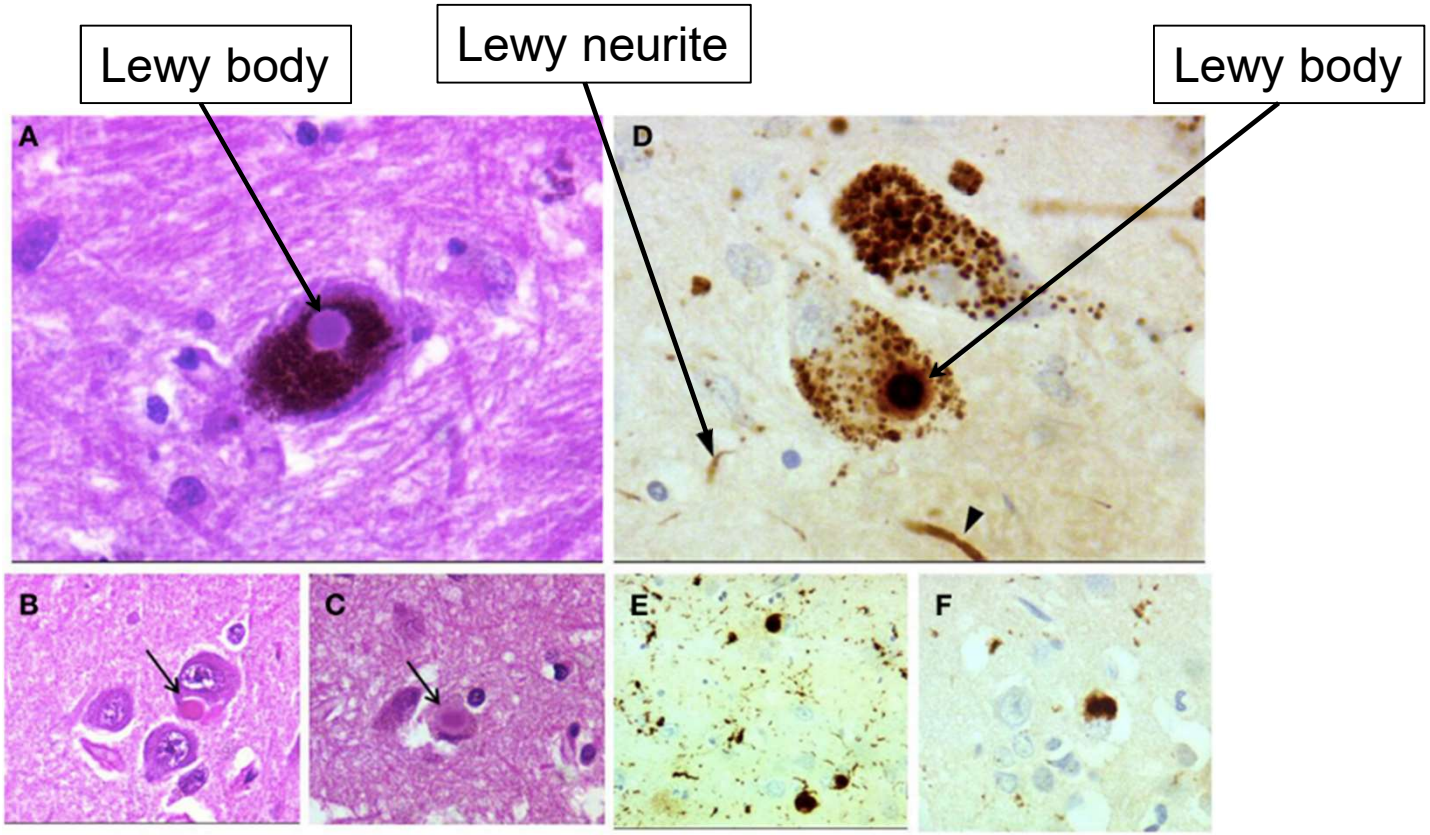
Deposits of α-synuclein



A) Lewy body in a neuron of the substantia nigra, B) in a pyramidal cell of CA1 area of the hippocampus, and C) in cingulated cortex (C) (arrows). Lewy body (arrow) and Lewy neurites (arrowheads) in the substantia nigra (D). Cortical Lewy bodies (E,F). (A–C) hematoxylin–eosin; (D–F) anti-α-synuclein immunostaining.

Taipa R et al. *Front Neurol*. 2019

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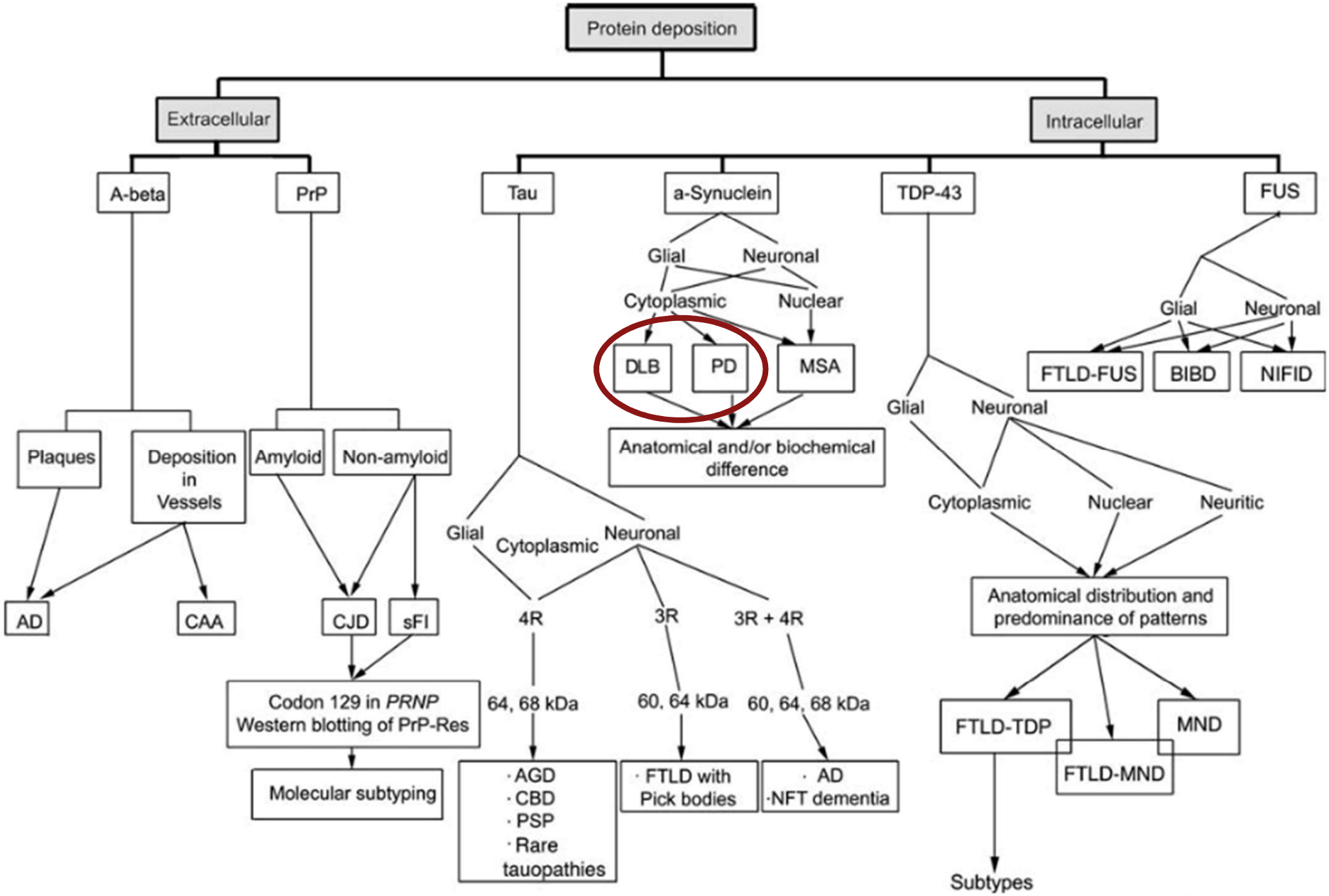

Kovacs GG et al. *Acta Neuropathol*. 2010

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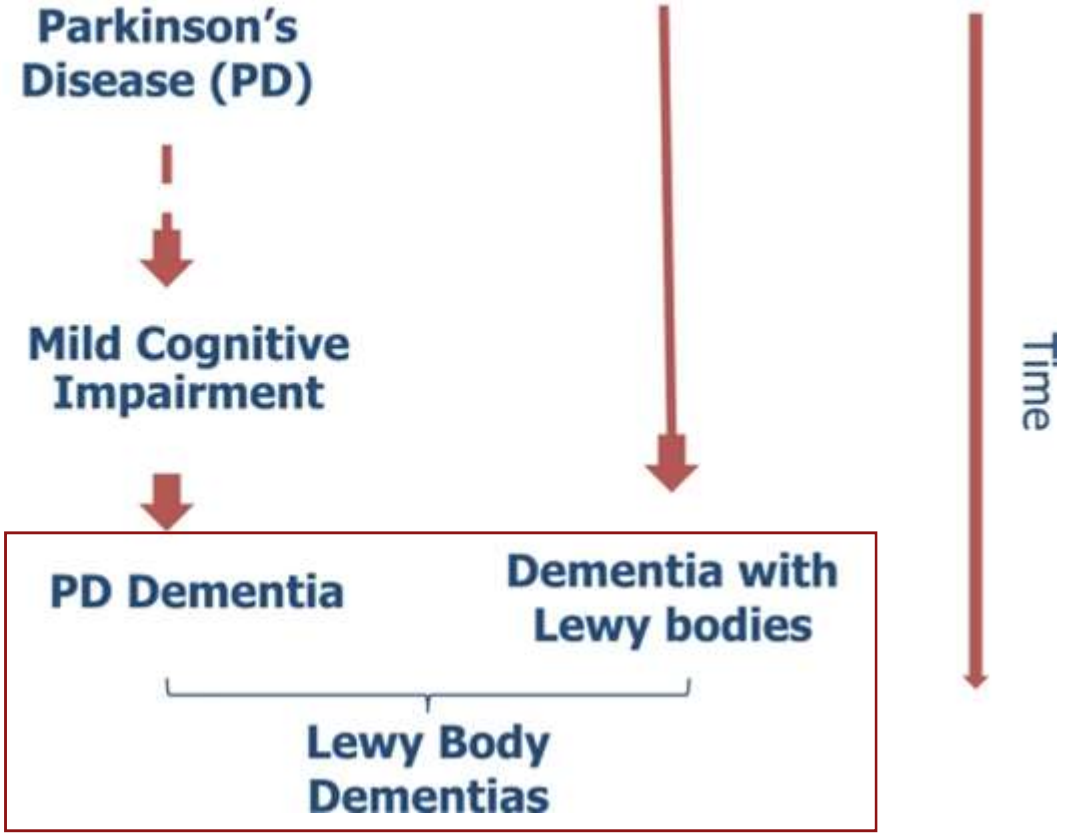
LBD = PDD or DLB



Modified from Donaghy PC et al. *Alzheimers Res Ther*. 2014

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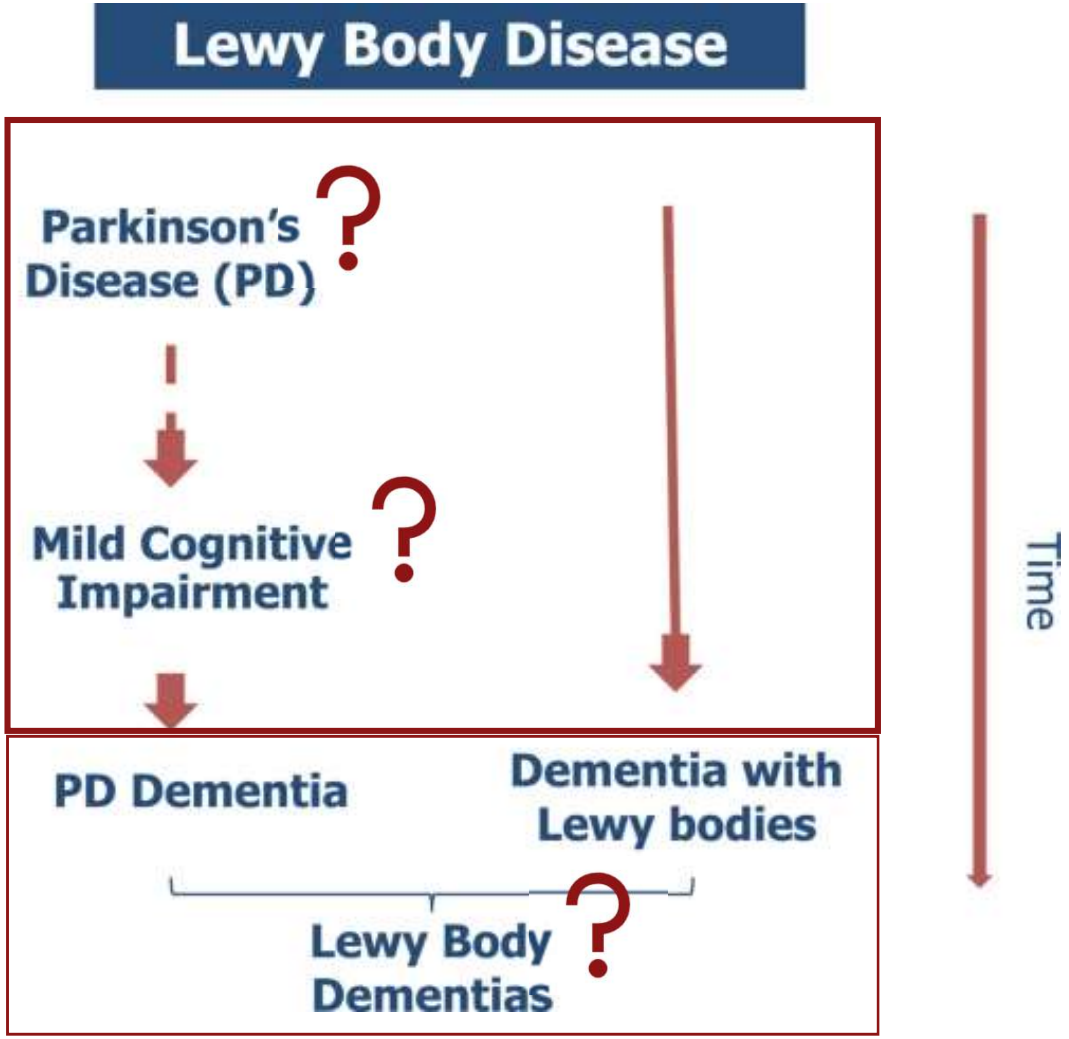
Continuum



Donaghy PC et al. *Alzheimers Res Ther*. 2014

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Cognitive impairment

3 key questions

1

Is there a cognitive complaint or change (according to the patient, a friend/family, or the physician)?

2

On cognitive tests: are they below expected for age and education level?

3

Does their cognition limit any of their Activities of Daily Living?

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Normal cognition

1

Is there a cognitive complaint or change (according to the patient, a friend/family, or the physician)?

2

On cognitive tests: are they below expected for age and education level?

3

Does their cognition limit any of their Activities of Daily Living?

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Mild cognitive impairment

1

Is there a cognitive complaint or change (according to the patient, a friend/family, or the physician)?

2

On cognitive tests: are they below expected for age and education level?

3

Does their cognition limit any of their Activities of Daily Living?

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Dementia

1

Is there a cognitive complaint or change (according to the patient, a friend/family, or the physician)?

2

On cognitive tests: are they below expected for age and education level?

3

Does their cognition limit any of their Activities of Daily Living?

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Slow & Progressive

Normal cognition **Mild cognitive impairment** **Dementia**

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Take home messages 1

1. Lewy body dementia is a neurodegenerative disorder.
2. Etiology: abnormal deposits of alpha-synuclein protein (*Lewy bodies* and *Lewy neurites*).
3. Neurodegenerative disorder model → **Continuum**.
   - It is important to identify patients at the early stages of the disease.
4. Lewy body dementias = dementia with Lewy bodies and Parkinson's disease dementia.

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Diagnosis of Lewy body dementia

PART B

Dementia with Lewy bodies

Fourth consensus criteria for probable and possible dementia with Lewy bodies		
Essential	**Dementia**	
	Clinical features	**Biomarkers**
Core	Recurrent visual hallucinations Fluctuating cognition REM sleep behavior disorder One or more spontaneous cardinal features of parkinsonism: bradykinesia, rest tremor or rigidity	Decreased dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET Decreased uptake ^{123}iodine-MIBG myocardial scintigraphy Polysomnography confirmation of REM sleep behavior disorder
Supportive	Severe sensitivity to antipsychotic agents Postural instability Syncope or other transient episodes of unresponsiveness Systematized delusions Hallucinations in other modalities Repeated falls Severe autonomic dysfunction Hypersomnia Apathy, anxiety and depression Hyposmia	Relative preservation of medial temporal lobe structures on CT/MRI Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/tetha range

McKeith I et al. Neurology. 2017

Dementia occurs before or concurrently with parkinsonism

Parkinson's disease dementia

Criteria for diagnosis of probable and possible PD-D

Probable PD-D

I. Core features: both most be present
- Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria.
- A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination.

II. Associated clinical features:
- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis.

III. Features which do not exclude PD-D, but make the diagnosis uncertain:
- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging.
- Time interval between the development of motor and cognitive symptoms not known.

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D.

Possible PD-D

I. Core features: both most be present

II. Associated clinical features:
- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention.
- Behavioral symptoms may or may not be present.

OR

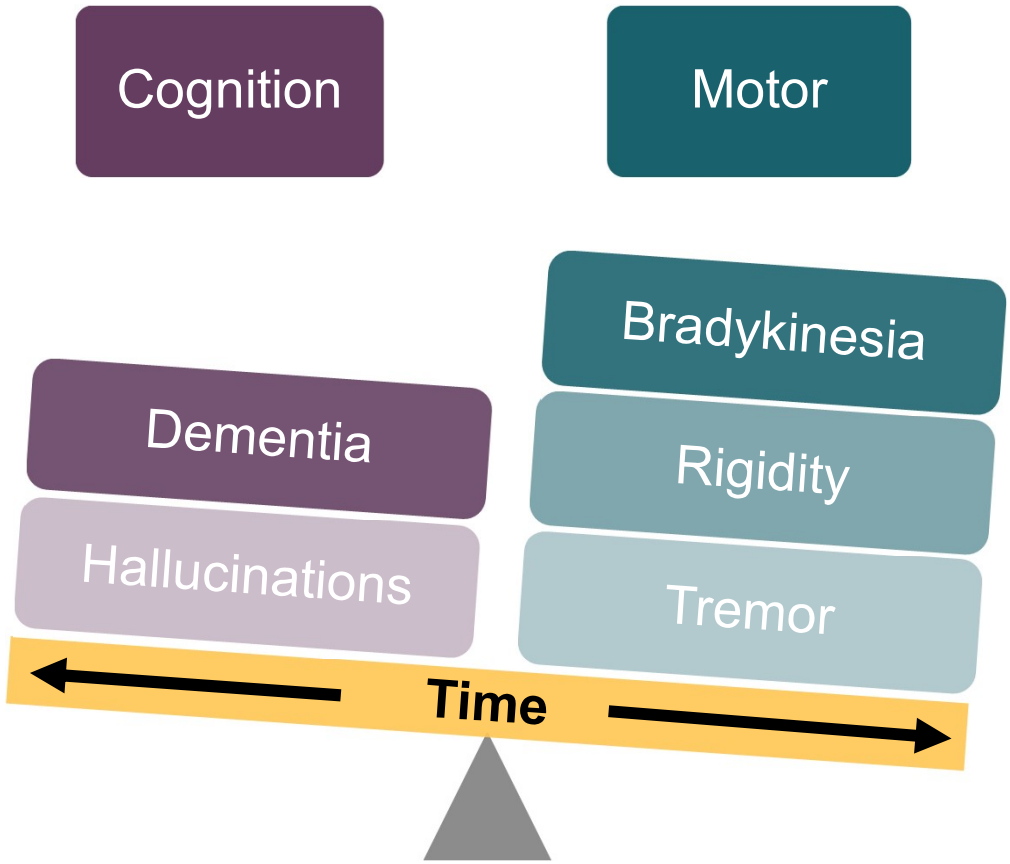
I. One or more of the group III features present.

II. None of the group IV features present.

Emre M et al. Mov Disord. 2007

Dementia occurs in the context of well-established Parkinson's disease

What is the difference between Parkinson's disease dementia and Dementia with Lewy bodies?



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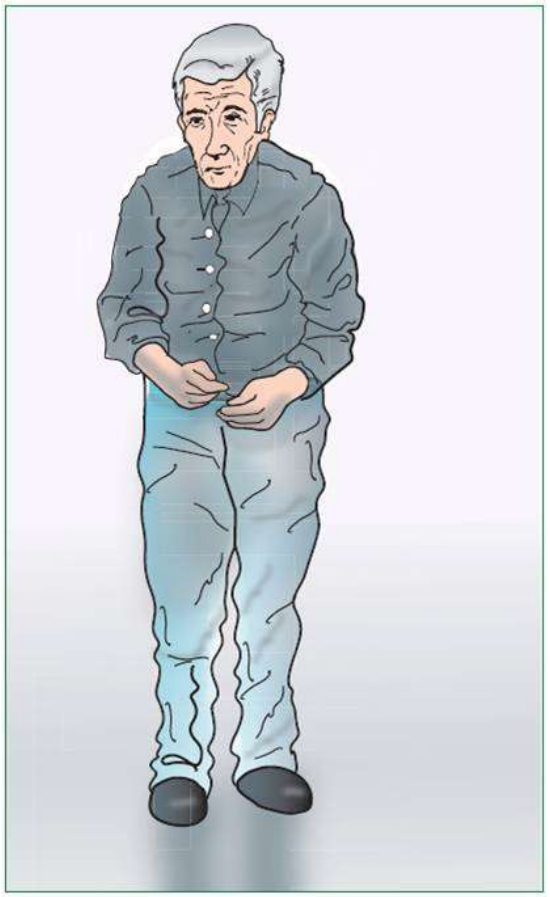
Parkinson's disease dementia

Parkinsonism

- Bradykinesia (slow, low amplitude movement)
- Rigidity (increased muscle tone to passive movement)
- Tremor (primarily in the resting position)
- Abnormal Gait and Posture



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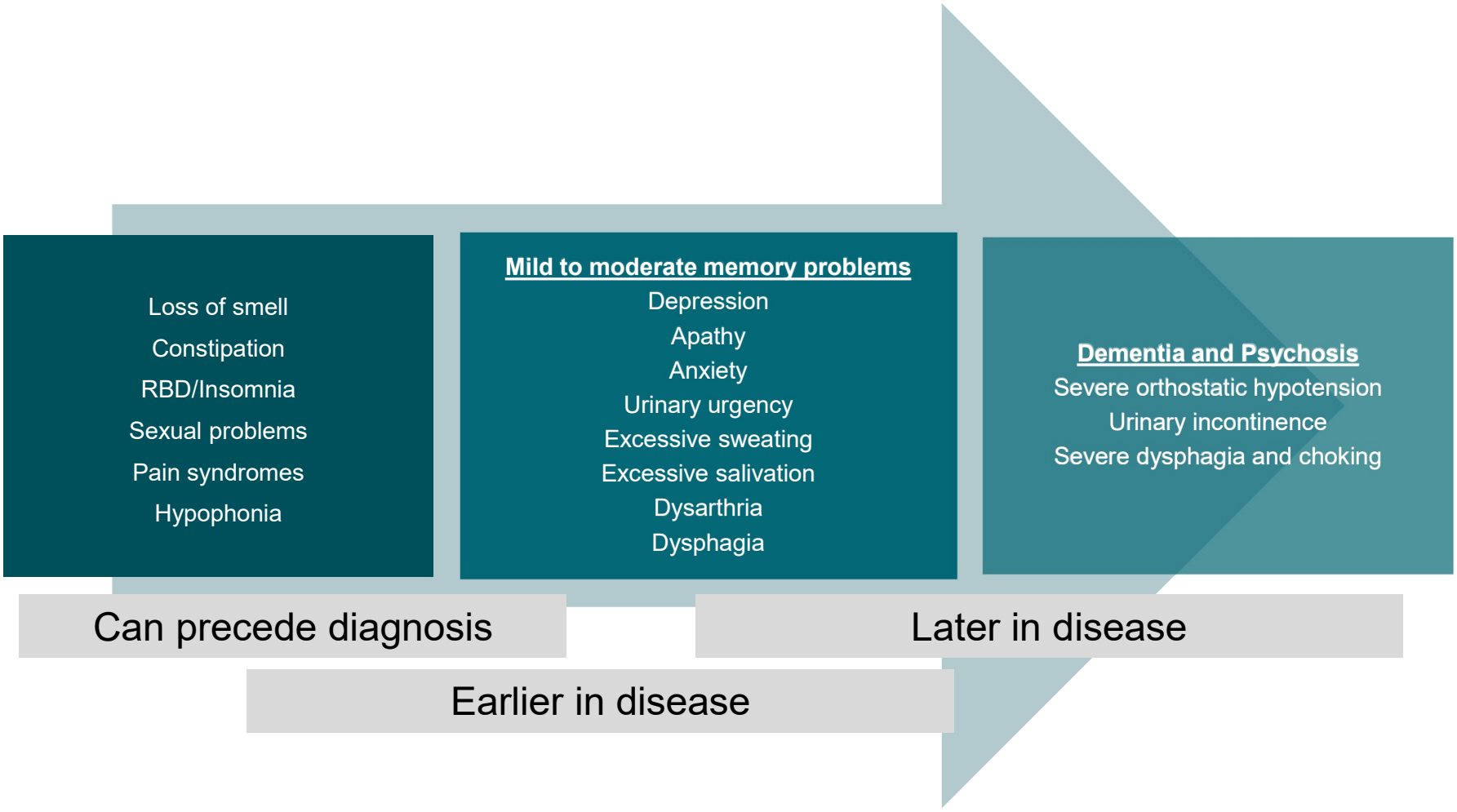
The spectrum of PD non-motor features



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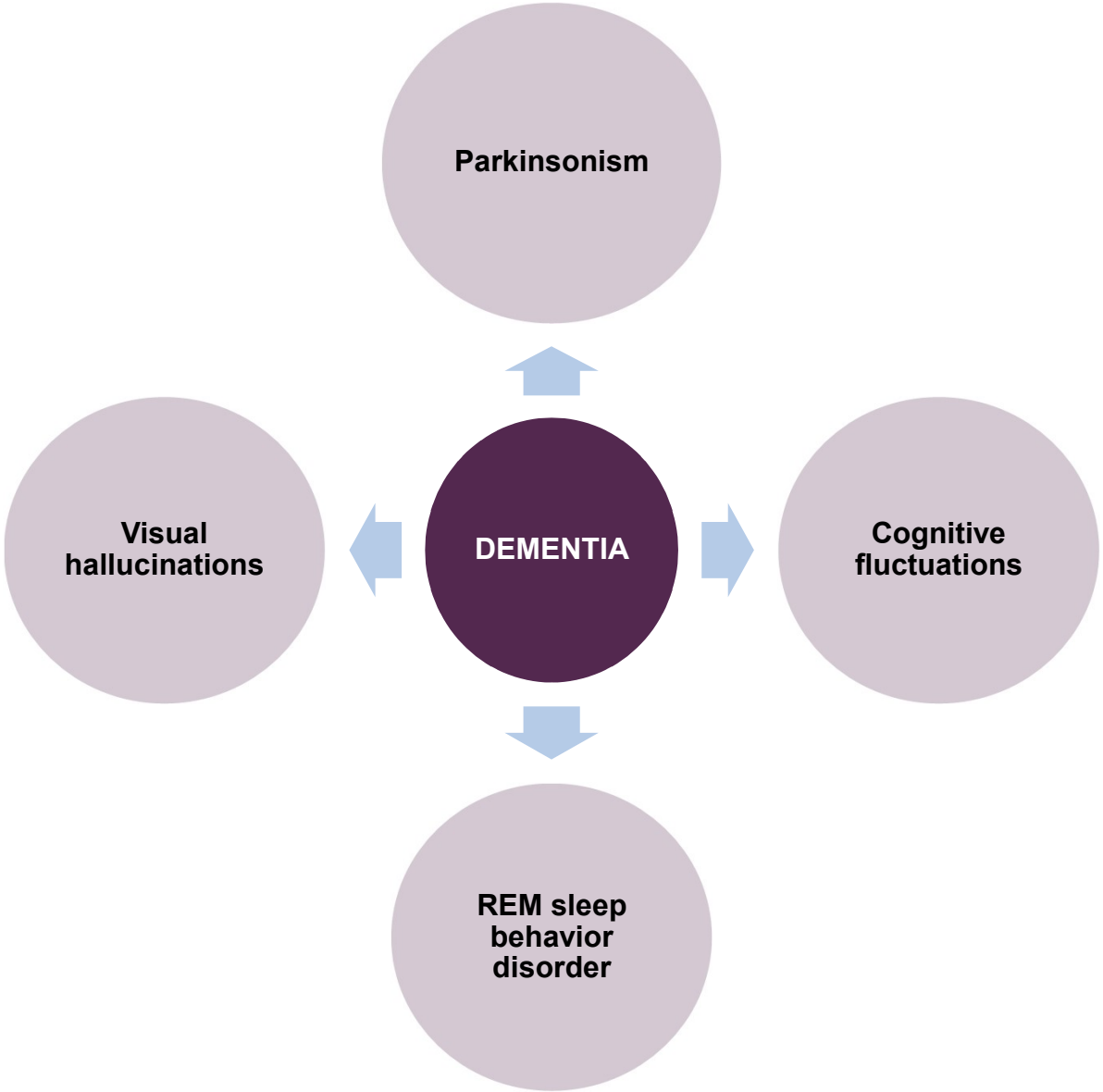
Dementia with Lewy bodies



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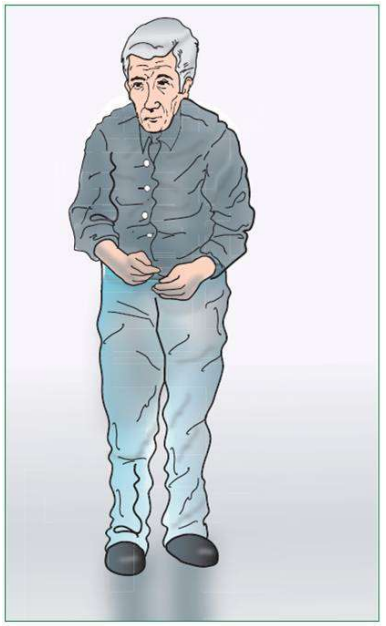
Core features of Dementia with Lewy bodies

One or more spontaneous cardinal features of parkinsonism: these are *bradykinesia* (defined as slowness of movement and decrement of amplitude or speed), *rest tremor*, or *rigidity*.

Postural instability, hypomimia (facial masking) and gait disturbances.



Medical history.
Physical and neurological examination.

Sometimes very responsive to levodopa.

Parkinsonism

Core features of Dementia with Lewy bodies

Spontaneous alterations in cognition, attention, and arousal.

They include waxing and waning episodes of behavioral inconsistency, incoherent speed, variable attention, or altered consciousness that involves staring or zoning out.

Difficult differentiation from Alzheimer's disease patients.

Medical history: questions about daytime drowsiness, lethargy, staring into space, or episodes of disorganized speech.
May occur in advanced stages.

Acetylcholinesterase inhibitors: Donepezil (Aricept), Rivastigmine (Exelon)
Memantine: improves attention.

Cognitive fluctuations

Core features of Dementia with Lewy bodies

Parasomnia: dream enactment behavior that includes movements mimicking dream content and associates with an absence of normal REM sleep atonia (muscle paralysis).

Medical history: bed partner, potential injuries.

Questionnaires.

Differentiate: confusional awakenings, severe obstructive sleep apnea, and periodic limb movements.

REM sleep behavior disorder

Melatonin.

Clonazepam.

- Caution: risk of worsening cognition and gait impairment.

Core features of Dementia with Lewy bodies

Recurrent, complex **visual hallucinations** are present in about 80% of patients.
Typically well-formed, featuring people, children, or animals.
Can be accompanied by related phenomena like passage hallucinations, sense of presence, and visual illusions.

Visual hallucinations

Medical history: ask the patient.
Questionnaires.

Avoid use of antipsychotics.

Non-pharmacological interventions.

Pimavanserin (Nuplazid):

- Takes 2-4 weeks to start working

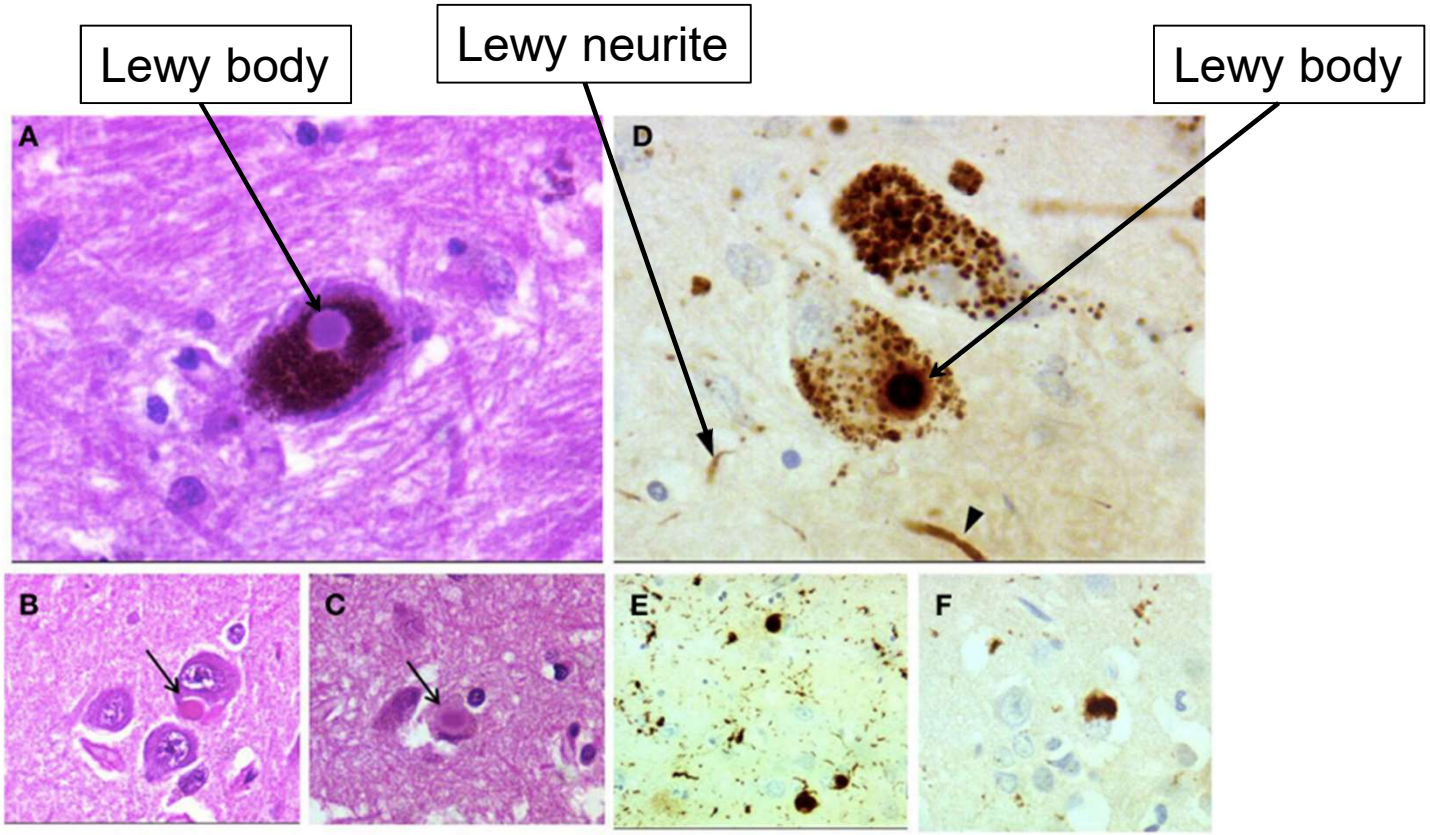
Low-dose Quetiapine:

- Not FDA-approved for Lewy body associated psychosis but is often used off label and can be helpful.
- Can cause sedation.

Cholinesterase InhibitorsDonepezil (Aricept), Rivastigmine (Exelon)

- Off-label usage but can be helpful in some patients.

Deposits of α-synuclein



A) Lewy body in a neuron of the substantia nigra, B) in a pyramidal cell of CA1 area of the hippocampus, and C) in cingulated cortex (C) (arrows). Lewy body (arrow) and Lewy neurites (arrowheads) in the substantia nigra (D). Cortical Lewy bodies (E,F). (A–C) hematoxylin–eosin; (D–F) anti-α-synuclein immunostaining.

Taipa R et al. *Front Neurol*. 2019

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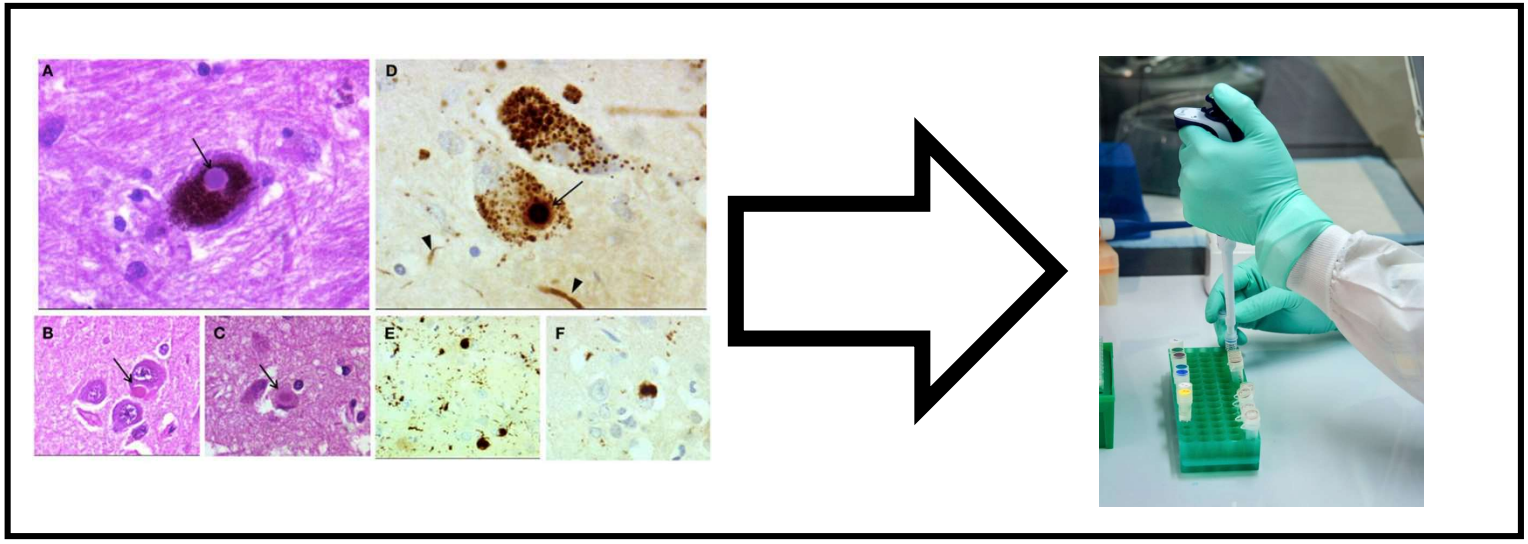
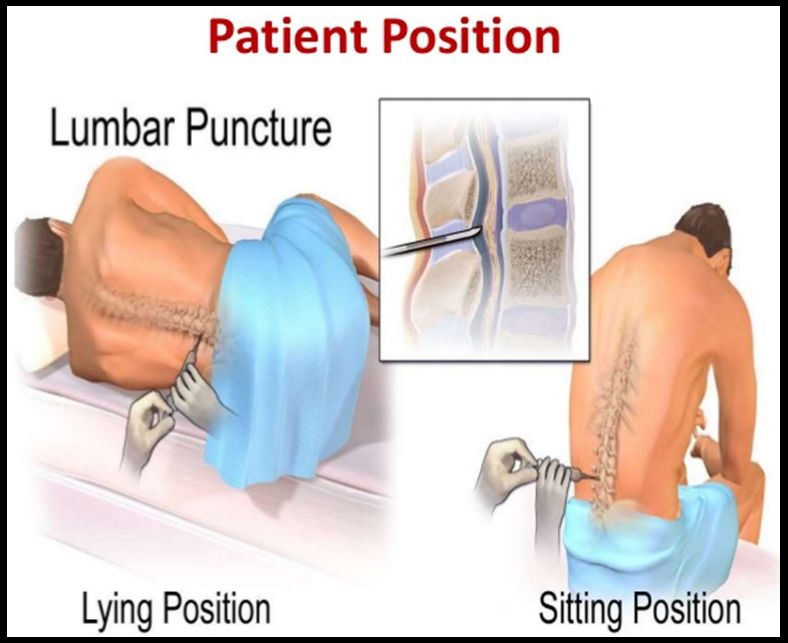
What is the status of assessing α-synuclein pathology in living people?

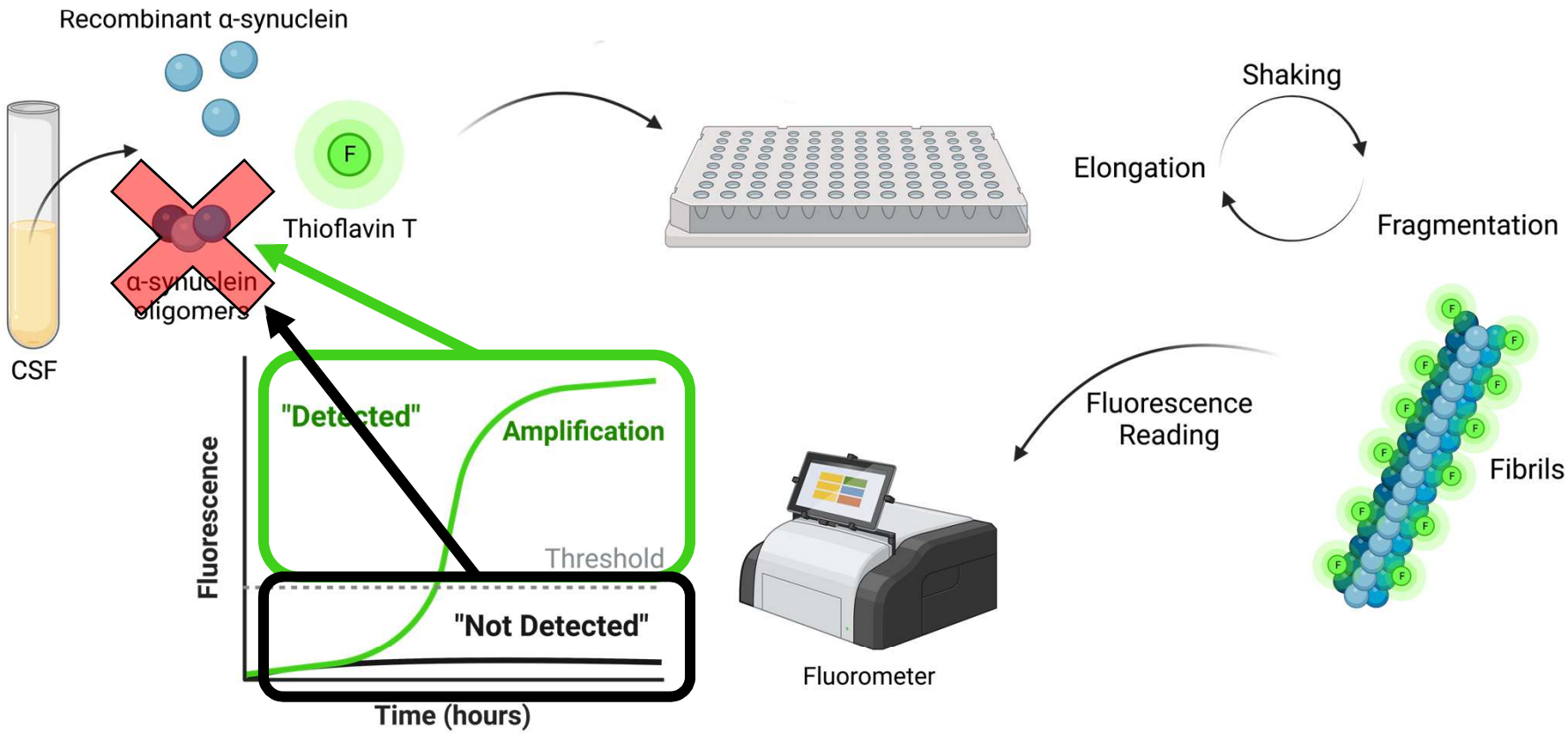


- Traditional ELISA-based assays trying to detect α-synuclein in people living with Parkinson's disease has had limitations
- The new biomarker addresses these limitations and can finally detect α-synuclein in living people.

- Requires a lumbar puncture (or spinal tap), which is done by a physician.
- Physician removes a few tablespoons of cerebrospinal fluid (CSF).
- CSF can be studied for different proteins or other chemicals that come from the brain.

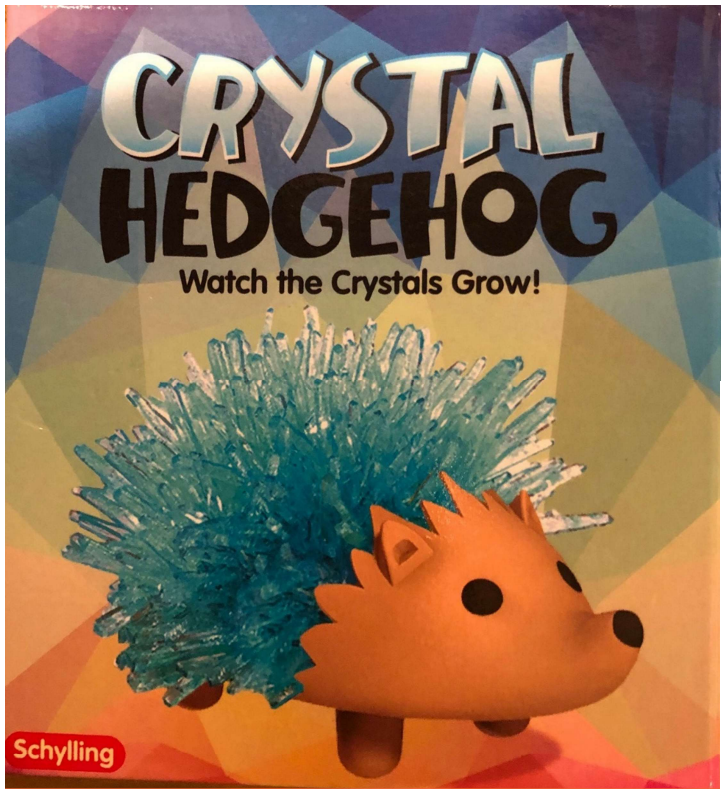


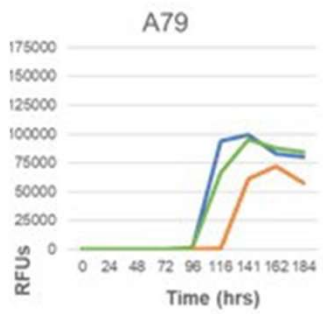
Seed Amplification Assay (SAA) Background



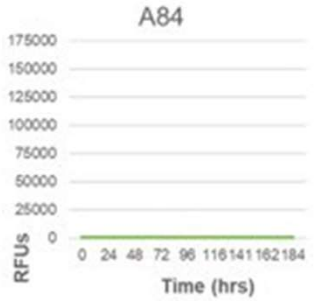
Seed Amplification Assay (SAA) = RT-QuIC and PMCA assays

Real-Time Quaking-Induced Conversion (RT-QuIC) and Protein-Misfolding Cyclic Amplification (PMCA)



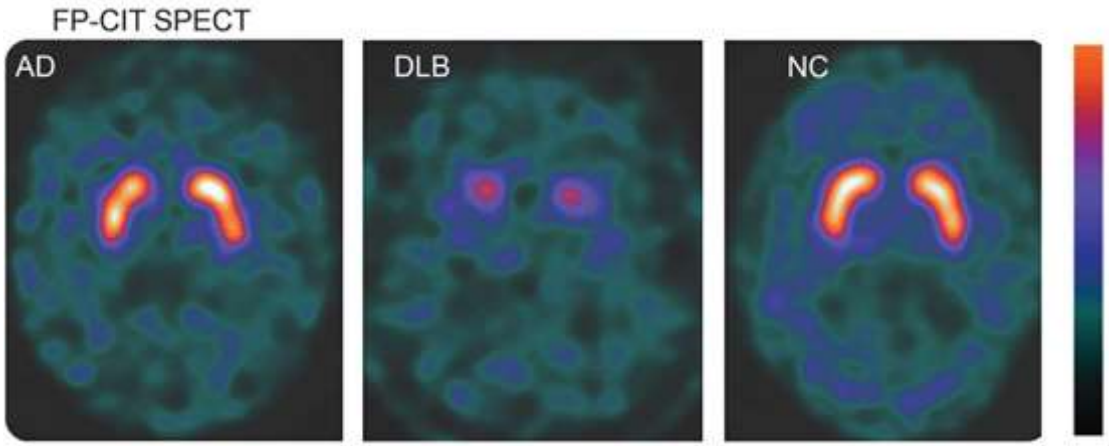


Detected

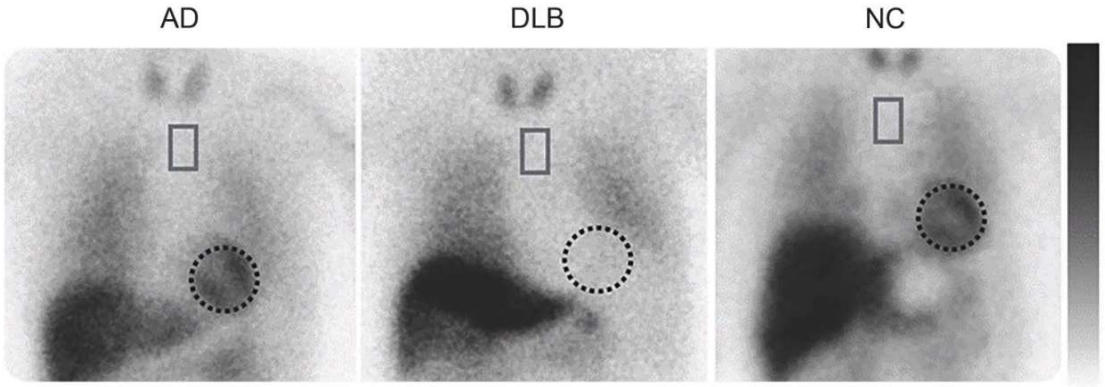


Not Detected

Indicative biomarkers in Lewy body dementias



Reduced dopamine transporter uptake in basal ganglia demonstrated by **SPECT** or **PET**.



Abnormal (low-uptake) in ^{123}Iodine-metaiodobenzylguanidine myocardial imaging **(MIBG)**

McKeith I et al. Neurology. 2017

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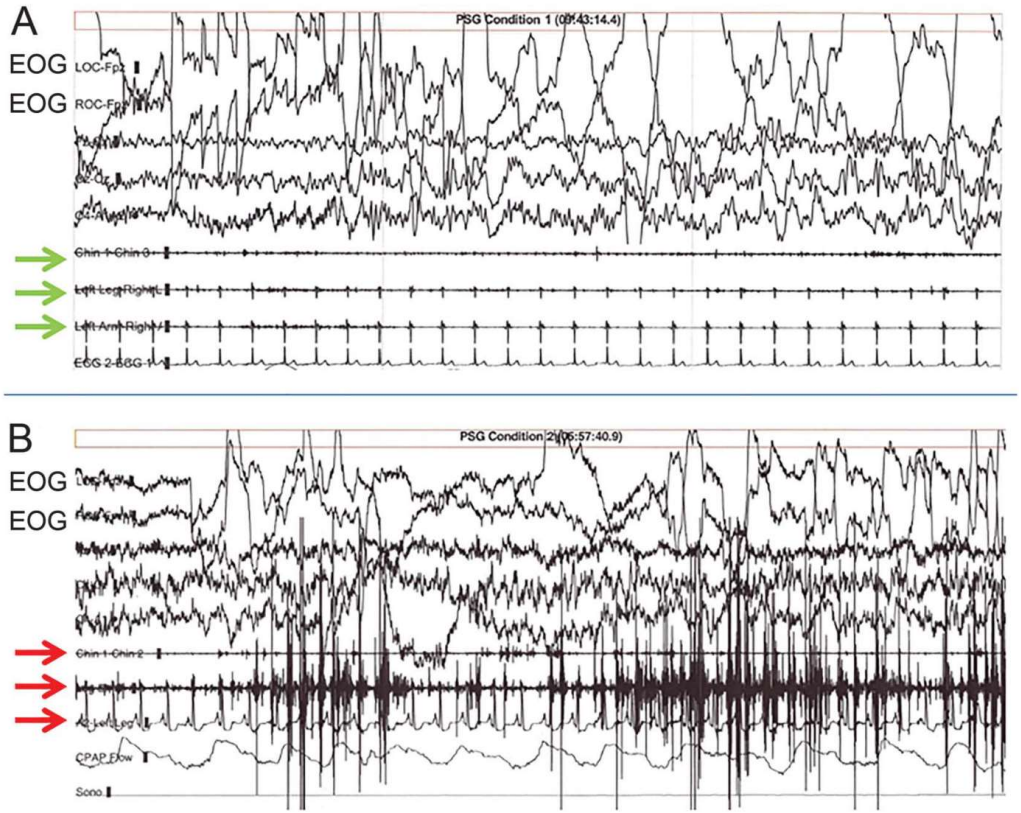
Indicative biomarkers in Lewy body dementias

Polysomnography confirmation of REM sleep without atonia.

(A) PSG recordings of normal REM sleep.
(B) REM sleep without atonia, typical of REM sleep behavior disorder.



McKeith I et al. Neurology. 2017

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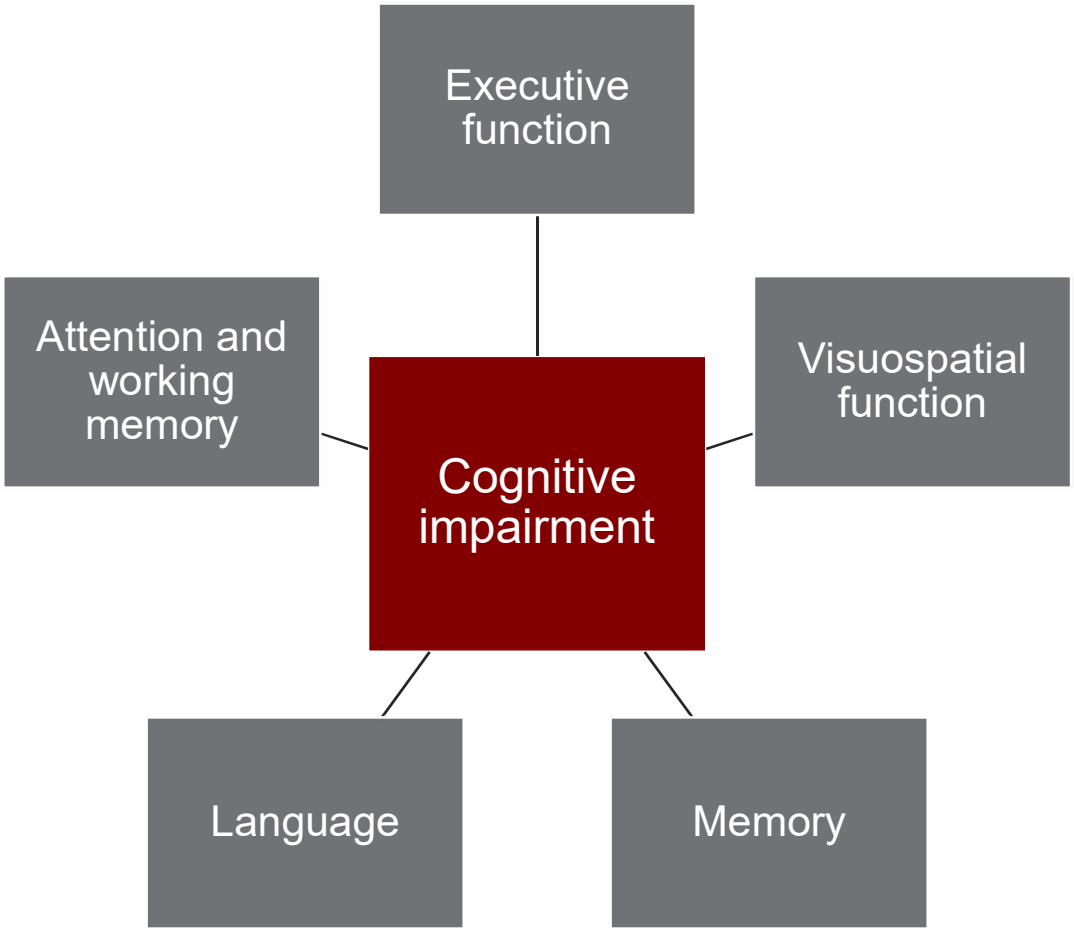
Profile of cognitive impairment in Lewy body dementias



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Medications for cognition

- Drugs originally developed for Alzheimer's disease have been tested in Lewy Body Dementias.
- Cholinesterase inhibitors:
  - Donepezil (Aricept)
  - Rivastigmine (Exelon) – pill or patch
  - Galantamine (Razadyne)
  - Watch for GI side effects (diarrhea)
- NMDA receptor antagonists show mixed results:
  - Memantine (Namenda)

Available tools

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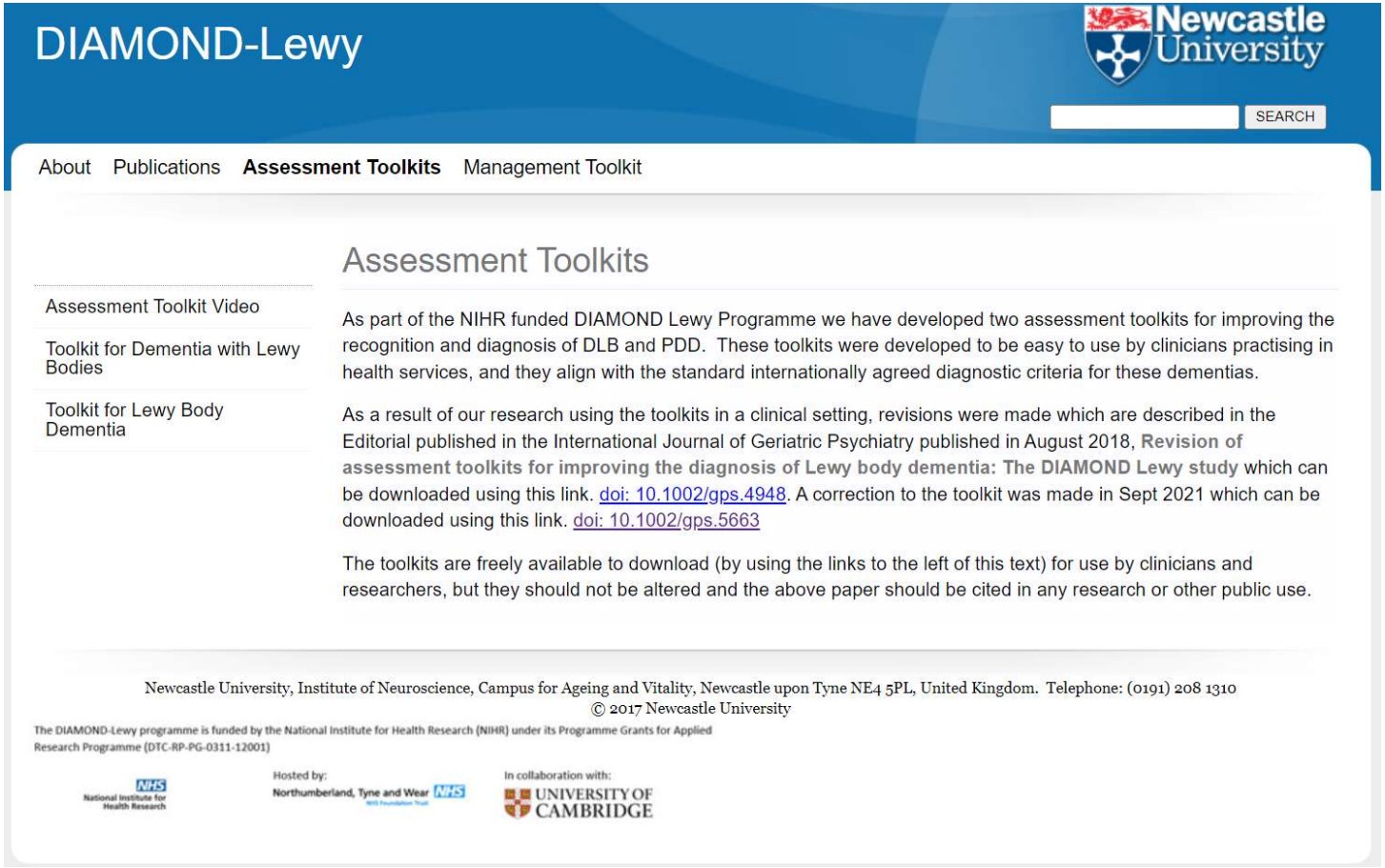
Toolkit for Lewy Body Dementia



https://research.ncl.ac.uk/diamondlewy/assessmenttoolkits/

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LBD Diagnostic Symptoms Checklist

Patient Instructions

Add a check mark next to any symptoms you are experiencing. Bring this form with you to your next appointment or send it to the doctor in advance. For more information on Lewy body dementia please visit www.lbda.org.

	Cognitive Symptoms
	Forgetfulness
	Trouble with problem solving or analytical thinking
	Difficulty planning or keeping track of sequences (poor multi-tasking)
	Disorganized speech and conversation
	Difficulty with sense of direction or spatial relationships between objects
	Fluctuations
	Fluctuating levels of concentration and attention
	Unexplained episodes of confusion
	Excessive daytime sleepiness
	Parkinson's-like Symptoms
	Rigidity or stiffness
	Shuffling walk
	Balance problems or repeated falls
	Tremor
	Slowness of movement
	Decrease or change in facial expression
	Change in posture
	Behavior and Mood Changes
	Hallucinations - Seeing things that are not really present
	Sleep Concerns
	Acting out dreams during sleep, sometimes violently, falling out of bed
	Reactions to Medications for Hallucinations (antipsychotics)
	Increased parkinsonism (stiffness, rigidity, etc.)
	Increased confusion
	Increased sleepiness

LBDA
LEWY BODY DEMENTIA ASSOCIATION

For Physicians: There are two clinical diagnoses that fall within the Lewy body dementia spectrum. ***This form may be helpful in diagnosing one of those disorders, dementia with Lewy bodies (DLB).*** The other form of LBD is Parkinson's disease dementia (PDD). **For DLB, use: ICD 9 = 331.82; ICD 10 = G31.83 [F02.80** without behavioral features **or F02-81** with behavioral features].

When making a dementia diagnosis, check for medication side effects that may mimic LBD symptoms. A referral to a neurologist is recommended for a differential diagnosis.

2017 Criteria for the Clinical Diagnosis of Probable and Possible DLB

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities.

- Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
- Deficits on tests of attention, executive function and visuo-perceptual ability may be especially prominent and occur early.

Core clinical features

(NOTE: The first three 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.
- REM sleep behavior disorder (RBD) which may precede cognitive decline.
- One or more spontaneous cardinal feature of parkinsonism – these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Indicative biomarkers

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

To see examples of abnormal scan results:

McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017 Jul 4;89(1):88-100.

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, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety and depression.

Supportive biomarkers

- 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

A diagnosis of DLB is *less likely*:

- In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
- In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
- If parkinsonism only appears for the first time at a stage of severe dementia

https://www.lbda.org/wp-content/uploads/2017/09/2017_diagnostic_checklist_-_updated_criteria_v2_1.pdf

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Take home messages 2

1. Dementia with Lewy bodies and Parkinson's disease dementia share common symptoms. Differentiating between these two diseases relies on **which symptom presented first: cognitive or motor?**
   - Dementia with Lewy bodies: dementia occurs before or concurrently with parkinsonism.
   - Parkinson disease dementia: dementia occurs in the context of well-established Parkinson's disease.
2. Parkinson's disease patients present **motor** and **non-motor** symptoms.
3. The diagnosis of dementia with Lewy bodies is based on the presence of **core features**: parkinsonism, cognitive fluctuations, REM sleep behavior disorder, and visual hallucinations; **and indicative biomarkers**: dopamine transporter SPECT or PET, MIBG, and PSG, or now a lumbar puncture. There are available questionnaires to help in the diagnosis of dementia with Lewy bodies.

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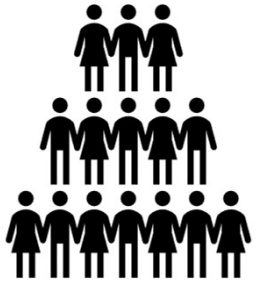
LBD patient's journey

PART C

Why is it important to diagnose LBD?



Second most common cause of neurodegenerative dementia after Alzheimer´s disease.

Heidenbrink JL et al. *J Geriatri Psychiatry Neurol*. 2002
Aarsland D et al. *Dement Geriatr Cogn Disord*. 2008

Underdiagnosed disease

Prevalence:
4.2-4.6% community
7.5% secondary care
20% neuropathological diagnosis

Vann Jones S et al. *Psychol Med*. 2014
Outeiro TF et al. *Mol Neurodegener*. 2019

Worse health indicators

↑ Mortality
↑ Functional impairment
↑ Impact in quality of life
↑ Healthcare costs
Earlier nursing home admission
↑ Rates of hospitalization

García-Ptacek S et al. *J Alzheimers Dis*. 2014
Mueller C et al. *Lancet Neurol*. 2017
Rongve A et al. *Int J Geriatric Psychiatry*. 2014

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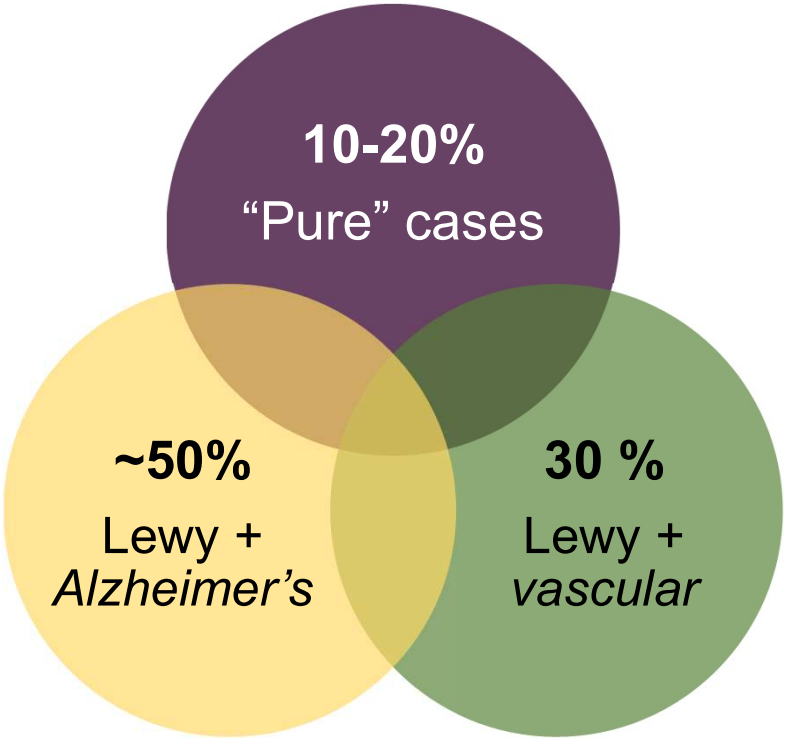
What makes the diagnosis of LBD so difficult?



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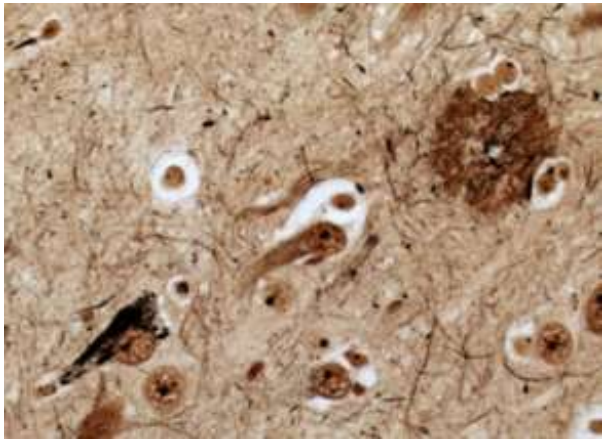
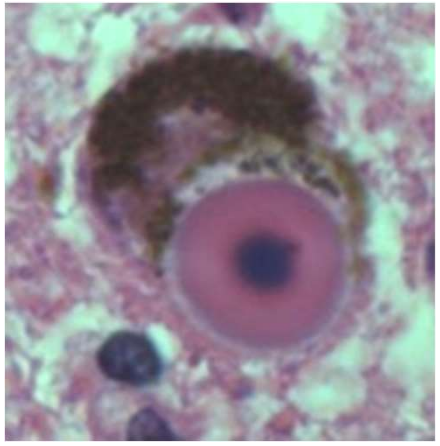
Where is the field going to help with the diagnosis?





CSF or (better) plasma or skin biomarker panels that include both Alzheimer's and Lewy body protein aggregation data together

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What can be done to help patients with Lewy body dementia?

1. Know what the problem is

2. Treat other conditions

3. Medications

4. Support

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Know what the problem is

- ✓Neuropsychological testing is used to **understand how a person is doing** in each cognitive domain.
- ✓Understanding the problem is the **first step** in **adapting** to it.
- ✓**Change** over time is **more helpful** than performance at one time point.

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Treat other conditions that make cognition worse

- ✓ Assess all **medications** (including medications prescribed for PD!) and their **side effect** profiles.
- ✓ Check for **infection** (like a Urinary Tract Infection).
- ✓ Measure **thyroid** function, vitamin **B12** levels.
- ✓ Evaluate for **depression**.
- ✓ Treat **dehydration** and **orthostatic hypotension**.
- ✓ Consider obstructive sleep **apnea** or **insomnia**.
- ✓ Correct **hearing loss**, **vision changes**, or **cataracts**.
- ✓ Encourage **exercise** and **social** engagement.

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Support

Encourage **support groups** for family and loved ones that specialize in the specific needs of Lewy body dementia.

Encourage **end of life discussions** early when the patient can be an active participant in expressing their wishes.

Consider a **palliative care** consultation.

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The Future

- Consider participating in research studies focused on understanding biomarkers that can help us find better treatments for Lewy body dementias

DID YOU KNOW

- 30% of all clinical trials fail to recruit a single person
- 85% of clinical trials face delays due to limited participation
- Fewer than 10% of Parkinson's or DLB patients ever take part in trials, despite overwhelming interest in working with scientists to help speed treatment breakthroughs

The Healthy Brain Aging Study

- NIH funded since 2015
- Goal is to understand mind and memory problems in Parkinson's disease, Alzheimer's disease and Aging
- People with Parkinson's disease who do not have memory problems and who have mild to moderate memory problems.
- We are also recruiting non-Parkinson's disease participants to understand age-related memory changes.
- 3 days the first year, then 1-2 days/year
- Research coordinator: Veronica Ramirez 650-721-2409

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A·D·R·C for healthy brain aging

Faceprint

- Goal is to develop a diagnostic tool for early detection of Lewy body diseases.
- A masked face is associated with the early stages of Parkinson's disease. By analyzing videos of facial movements, we hope to develop an algorithm to detect small differences in facial expression.
- We are recruiting participants with Mild Cognitive Impairment due to Lewy bodies or Dementia with Lewy bodies.
- 1 visit to campus for a 30-minute session.
- Research coordinator: Alena Smith 310-863-8108

alenaa@stanford.edu

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Take home messages 3

1. Lewy body dementia is the second most common cause of neurodegenerative dementia. Is often under or misdiagnosed, delaying the access of patients to proper management.
2. The diagnosis of Lewy body dementia is difficult because of the presence of co-pathologies that can decrease the frequency of core features, and the lack of disease-specific biomarkers.
3. To help patients with Lewy body dementia we need to know what the problem is, treat other conditions, start pharmacologic treatment (*when necessary*), and provide specialized support.

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Questions?

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