Dementia with Lewy Bodies

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Dr. Gill has no conflicts or professional relationships to disclose.

Learning objectives

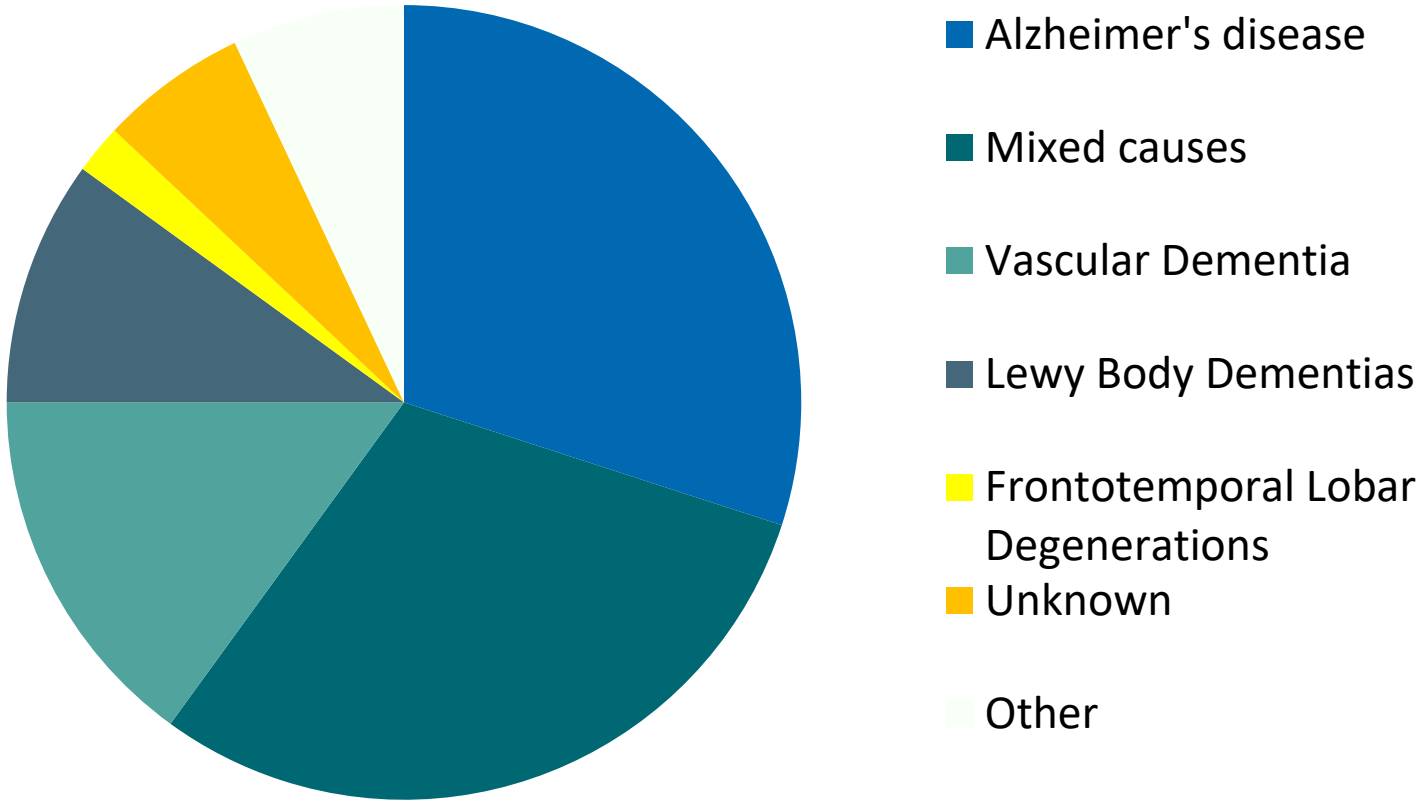
- Overview of parkinsonian dementias
- Diagnosis of dementia with Lewy bodies
- Pathophysiology of dementia with Lewy bodies
- Treatment

Sam

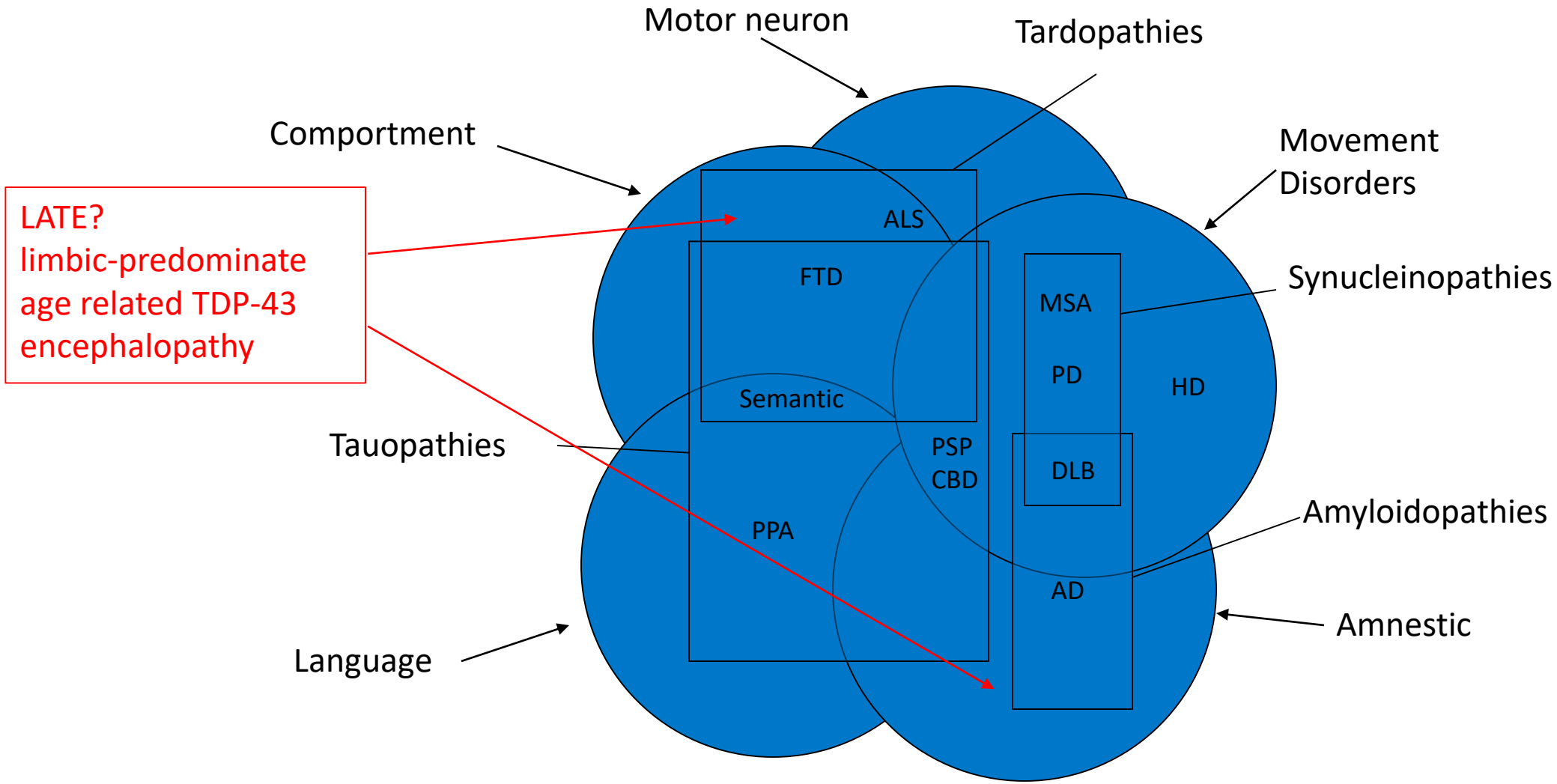
John

Joan

Estimated causes of dementia



Classification of Cognitive Disorders



ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; MSA = multisystem atrophy; Semantic = semantic dementia; PD = Parkinson's disease; HD = Huntingdon's disease; PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; PPA = primary progressive aphasia; AD = Alzheimer's disease

Parkinsonian dementias

Lewy bodies	Dementia with Lewy Bodies	Slowness of movement, tremor, and cognitive impairment. Generally do not respond well to carbidopa/levodopa
	Parkinson's disease with dementia	Same as dementia with Lewy bodies, but cognitive symptoms start one year or more after parkinsonism
	Multisystem atrophy	Slowness of movement, tremor and cognitive impairment along with lightheadedness when standing up and trouble controlling bladder. Generally also does not respond well to carbidopa/levodopa
Tau-opathies	Progressive Supranuclear Palsy	Wide-eyed stare, reduced eye blink frequency, back and neck stiffness. Generally also does not respond well to carbidopa/levodopa
	Corticobasal syndrome	Slowness of movement, tremor as well as stiffness, jerking movements and alien limb. Generally does not respond well to carbidopa/levodopa
	Frontotemporal dementia with parkinsonism	Parkinsonism variable, sometimes levodopa responsive, often similar findings to those in corticobasal syndrome
Amyloid-opathy	Alzheimer's disease	Parkinsonism tends to be later in course; rigidity, bradykinesia, tremor (resting or postural)
	Normal pressure hydrocephalus	Abnormal gait, cognitive impairment, urinary incontinence

Modified from Boeve, B. Neurol Clin. 2007

Sam

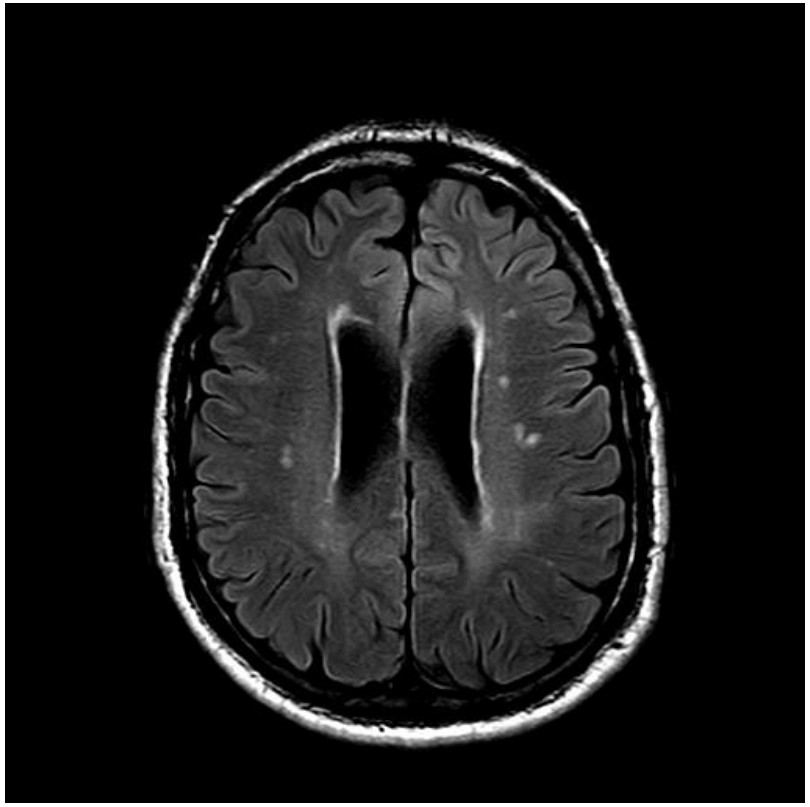
Sam is a 56 year old gentleman who developed forgetfulness and a right sided tremor about three years ago. Both of these have worsened over the past three years to the point where he is impaired by both his memory and slowness of movement.

He frequently sees dead relatives in the room with him and acts out his dreams violently.

His examination is remarkable for bradykinesia, resting tremor and cogwheel rigidity along with memory and executive dysfunction. MMSE 26/30

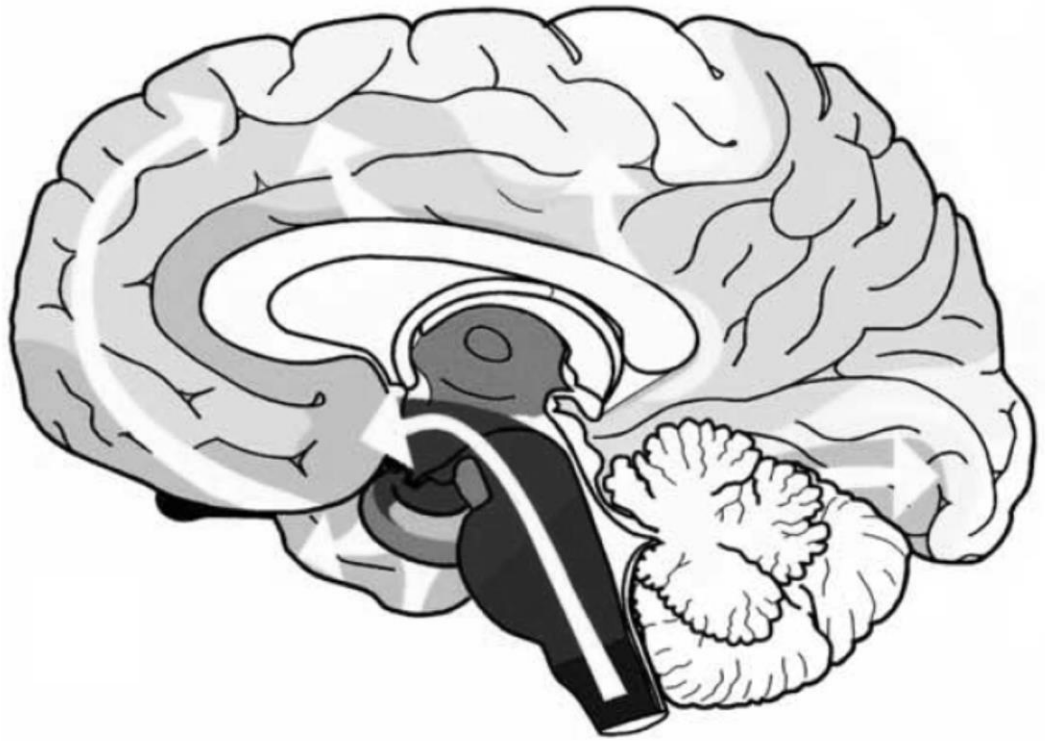
Sam continued

CBC, complete metabolic panel, and TSH are normal. B12 412.

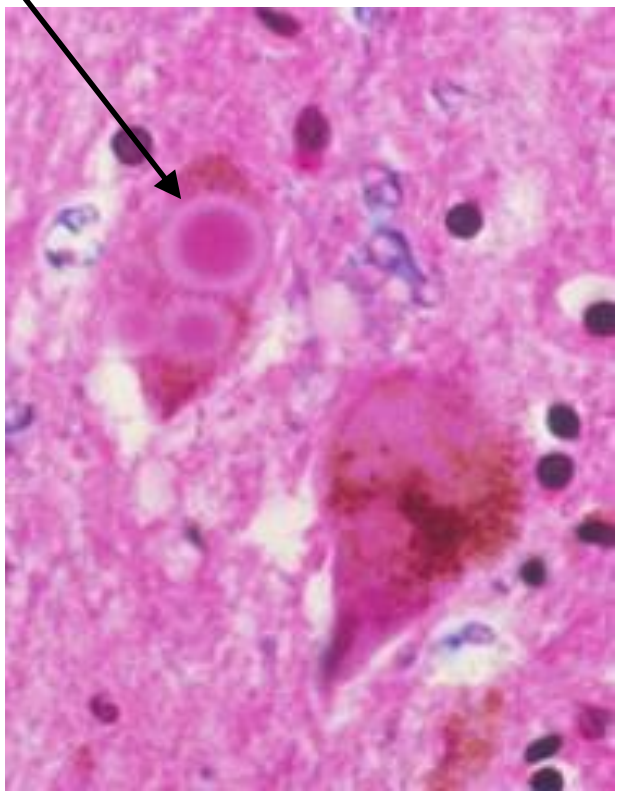


Diagnosis?

Lewy Bodies



Braak, et. al. Neurobiolg Aging. 2003



Lewy bodies contain Alpha synuclein protein, ubiquitin protein and others.
Role of ubiquitin is one of garbage disposal of proteins, alpha synuclein function is not known.

Diagnostic Criteria

Required Criterion

- Dementia, often with early and prominent deficits in attention, executive function, and visuoperceptual ability; prominent or persistent memory impairment tends to occur with progression.

Probable Dementia With Lewy Bodies

- Presence of two or more core clinical features (with or without indicative biomarker)
- One core clinical feature plus at least one indicative biomarker

Possible Dementia With Lewy Bodies

- Presence of one core clinical feature (no indicative biomarker)
- Presence of one or more indicative biomarkers but no core clinical features

Core Clinical Features

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations
- Rapid eye movement (REM) sleep behavior disorder (may precede other symptoms)
- Parkinsonism (defined as one or more spontaneous cardinal features: bradykinesia, rest tremor, rigidity)[b]

Supportive Clinical Features

- Severe sensitivity to antipsychotic agents
- Postural instability
- Repeated falls
- Syncope or other transient episodes of unresponsiveness
- Severe autonomic dysfunction (eg, constipation, orthostatic hypotension, urinary incontinence)
- Hypersomnia/excessive daytime sleepiness
- Hyposmia
- Hallucinations in nonvisual modalities
- Systematized delusions
- Apathy, anxiety, and depression

Indicative Biomarkers

- Reduced basal ganglia dopamine transporter uptake (SPECT or PET)
- Abnormal (low uptake) iodine 123-MIBG myocardial scintigraphy
- Confirmation of REM sleep without atonia on polysomnography

Supportive Biomarkers

- Relative preservation of medial temporal lobe structures on CT/MRI
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity and/or the cingulate island sign on FDG-PET imaging
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

CT = computed tomography; EEG = electroencephalogram; FDG-PET = fludeoxyglucose positron emission tomography; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

[a] Modified with permission from McKeith IG, et al, Neurology.[6] © 2017 The Authors.

[b] The parkinsonism in dementia with Lewy bodies occurs after or concurrent with dementia onset. If parkinsonism is the only core clinical feature and appears only in the context of severe dementia, dementia with Lewy bodies is less likely.

CONTINUUM: LIFELONG LEARNING IN NEUROLOGY

Armstrong MJ CONTINUUM. 2019.

Mayo Fluctuations Scale

1. Are there times when the patient's flow of ideas seems disorganized, unclear or not logical?
2. How often is the patient drowsy and lethargic during the day, despite getting enough sleep the night before?
   - All the time or several times a day*
   - Once a day or less
3. How much time does the patient spend sleeping during the day (before 7:00pm)
   - 2 hours or more*
   - Less than 2 hours
4. Does the patient stare into space for long periods of time?

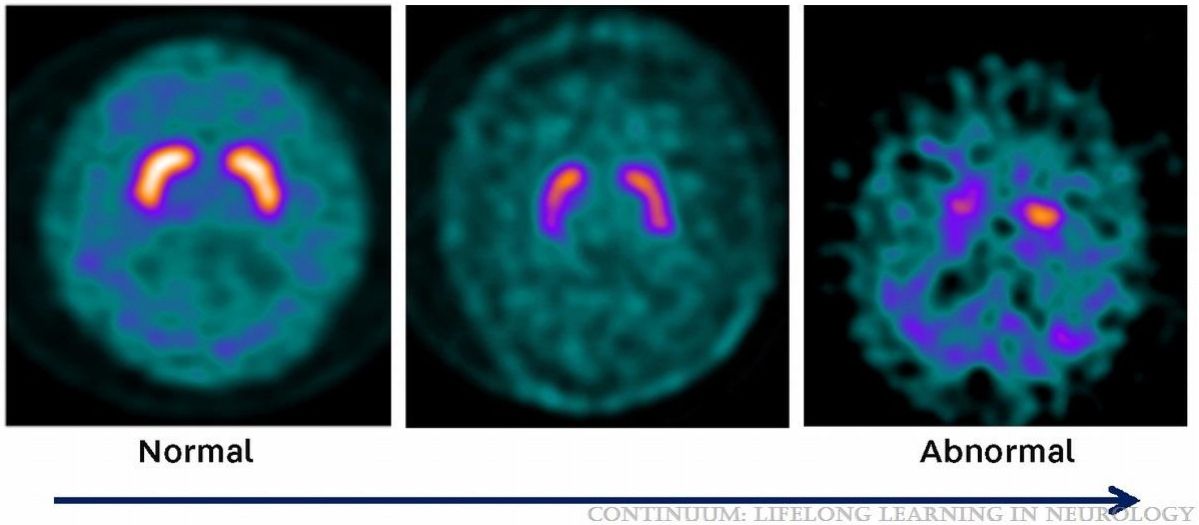
A score of 3 or 4: PPV of 83% for DLB vs. AD, and a score of <3: NPV of 70% for absence DLB in favor of AD.

Ferman, et. al. Neurology. 2004.

REM Behavior Sleep Disorder

- Movement of body and/or limbs associated with dreaming
- One of:
  - Potentially harmful sleep behavior
  - Acting out dreams
  - Behavior that disrupts sleep continuity

DaTscan



- Ioflupane ^{123}I tracer, aka phenyltropane
- Images striatal dopamine transporter
- FDA approved to distinguish essential tremor from Parkinsonian syndromes

How sure can we be?

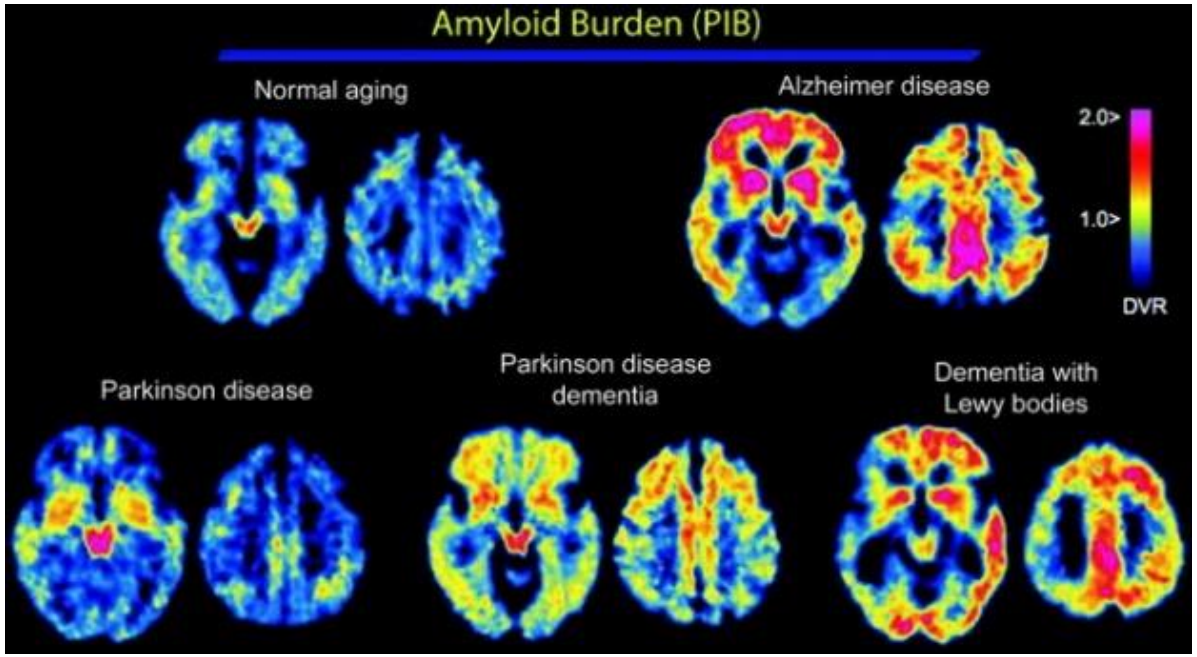
- No direct measurement of alpha Synucelin
- Prior clinical criteria: Sensitivity ~60%, specificity ~80% (sensitivity 88% when REM sleep behavior disorder counted as core feature)

- DaTscan: sensitivity 87%, specificity 72% DLB vs. AD
- MRI: Can show less hippocampal atrophy, but is not diagnostic
- FDG-PET: Can show occipital lobe hypometabolism, but not diagnostic
- Neuropsychologic testing can show differences, but not enough to discriminate
- CSF: Up to 25% of DLB patients have AD CSF profile

Ferman, et. al. Neurology. 2011; McKeith, et. al. 2007; Steenoven et. al. J Alzheimer's Dis. 2016

Why can’t we be more sure?

In vivo Amyloid imaging:



Gomperts, et. al. Neurology. 2008

Dementia with Lewy bodies or Parkinson's disease with dementia?

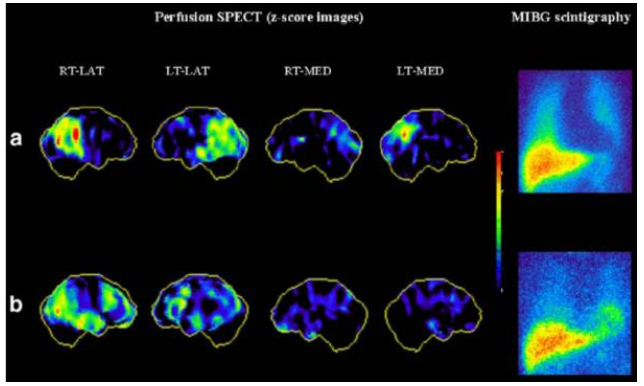
They are the same

- Similar parkinsonism, hallucinations, and fluctuations
- Indistinguishable by neuropsychology
- Indistinguishable by pathology at autopsy
- **Treatment is identical**

2017 criteria eliminated the one year rule and now most patients with one meet criteria for the other

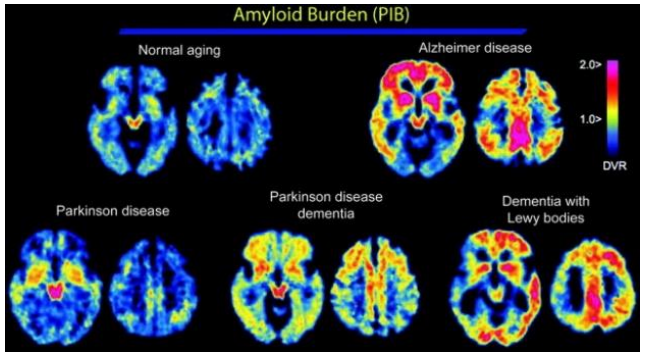
They are different

- Cardiac perfusion



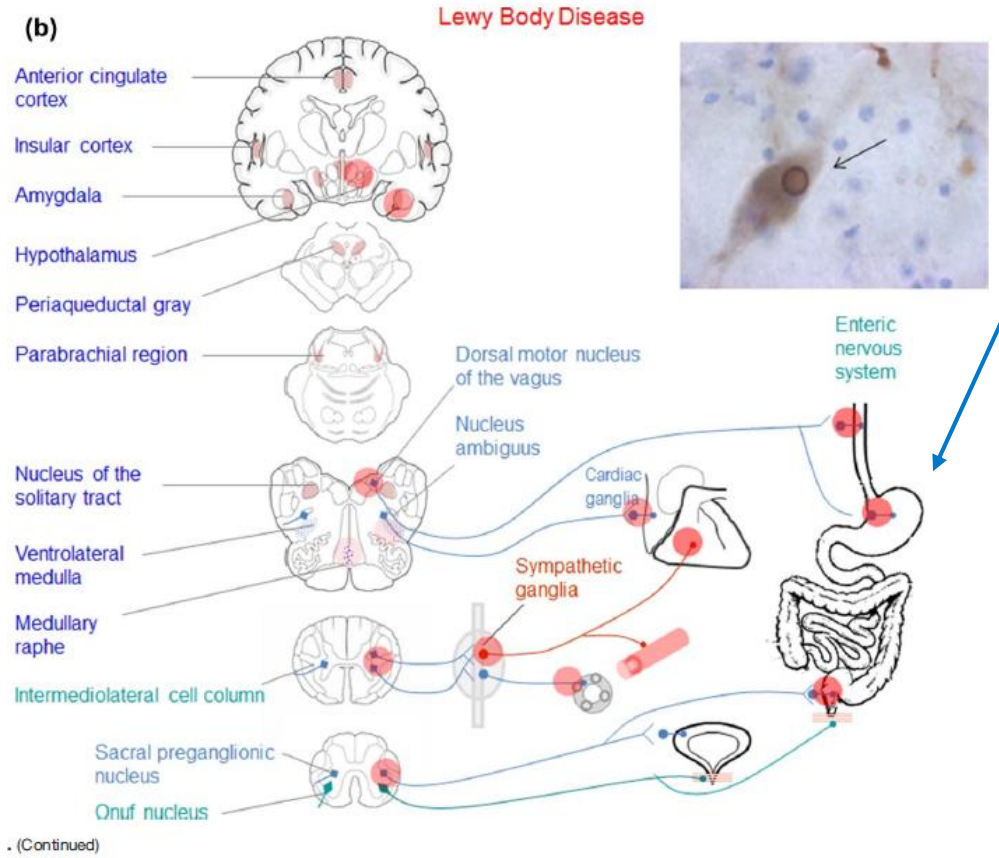
Hanyu, et. al. Eur J Nuc Med Mol Imaging. 2006

- In vivo amyloid imaging

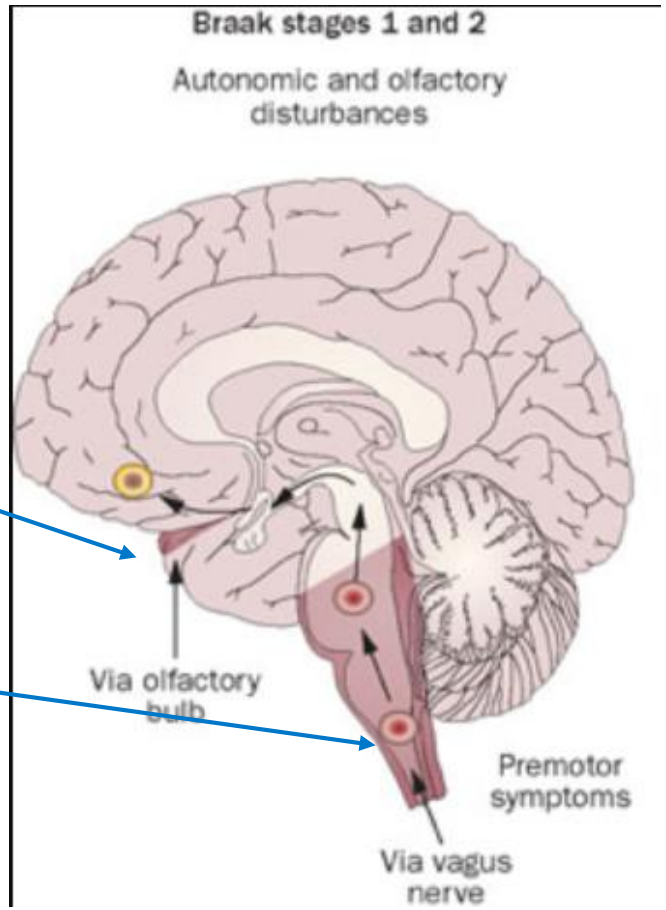


Gomperts, et. al. Neurology. 2008

Prodrome



1. Constipation
2. Olfactory dysfunction
3. REM sleep behavior disorder



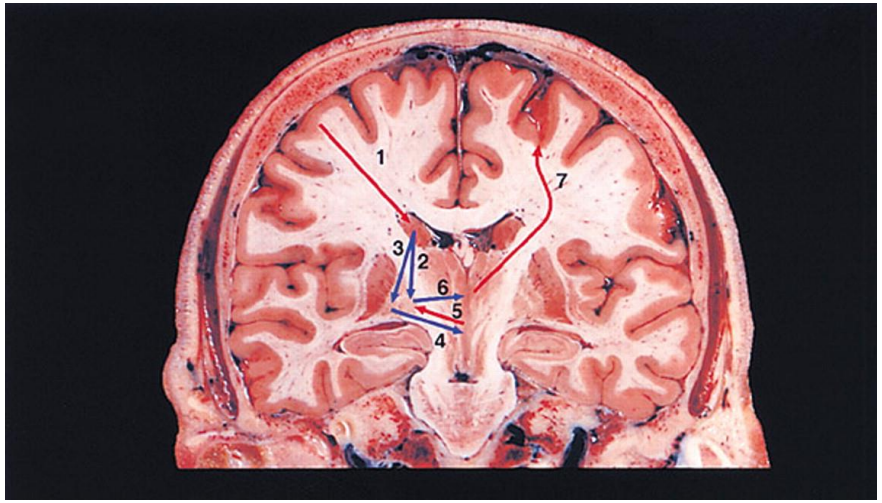
Coon, et. al. Mov Disord. 2018

Syndrome

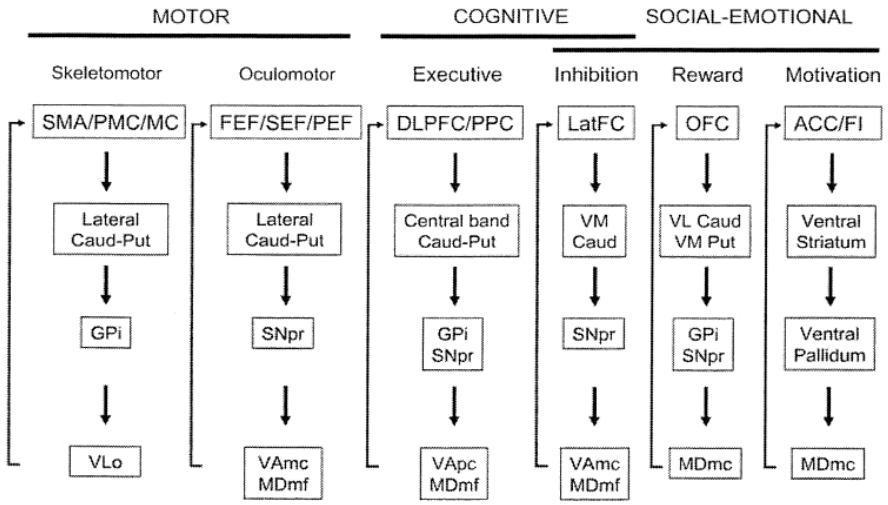
1. Cognitive impairment
2. Parkinsonism
3. Autonomic dysfunction

Associated features:

1. Visual hallucinations
2. Fluctuations
3. Depression/anxiety
4. Neuroleptic sensitivity



Litvan, I, et. al. Arch Neurol. 1998



Seeley, W. AAN Syllabus. 2008

Treatment (all off label)

Parkinsonism
- Levodopa

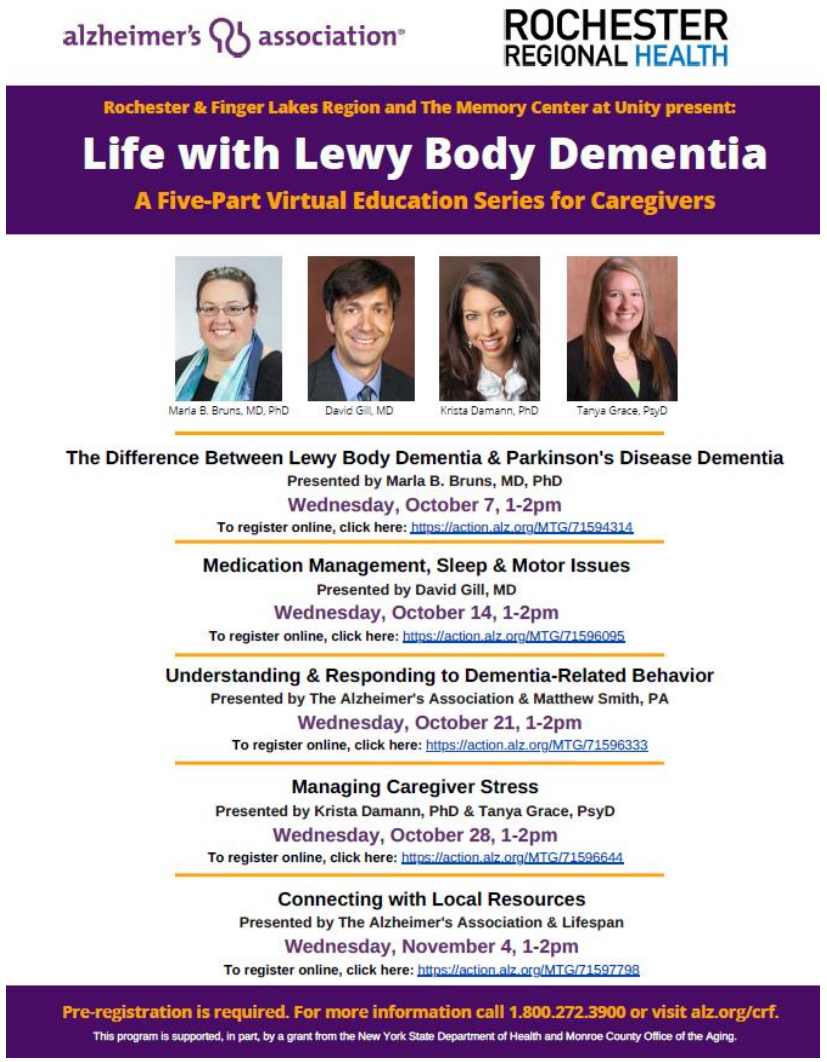
Cognitive impairment
- Cholinesterase inhibitors
- Namenda?

Hallucinations
- **ATYPICAL** antipsychotic medications (quetiapine, pimavanserin or clozapine)
- Cholinesterase inhibitors

REM sleep behavior disorder
- Clonazepam
- Melatonin

Support

- Alzheimer's Association
- Parkinson's Foundation
- Lewy Body Dementia Association
- Finger Lakes Caregiving Institute/Lifespan



Questions?