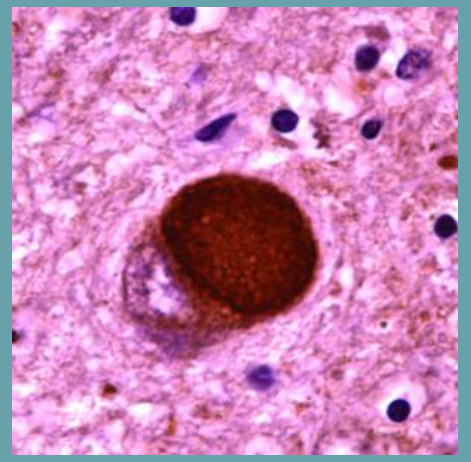

LEWY BODY DEMENTIA

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Saint Louis University School of Medicine

Disclosures

- Dr. Sanford has no relevant financial disclosures

Objectives

- Differentiate Lewy Body Dementia and Parkinson's Disease with dementia
- Understand the pathophysiology of Lewy Body Dementia and the role ∝-synuclein plays
- Learn how to recognize the symptoms and make a correct diagnosis
- Discuss current available treatment options

Case Presentation

- **HPI: 76 y/o WM presenting to the geriatric medicine clinic for evaluation of memory impairment and hallucinations**
  - *Gradual, worsening cognitive impairment for ~2 yrs*
  - *Started Aricept 2 yrs prior at first presentation, which lead to hallucinations*
  - *These resolved w/ cessation of Aricept but resumed ~6 mos prior to eval*
  - *Pt could not distinguish visual images from reality*
  - *Was unable to describe the hallucinations, but wife reported that he would usually see dwarfs or elves and the hallucinations were distressing*
  - *Several falls in past year. Unknown etiology. "I just fall"*

Case presentation

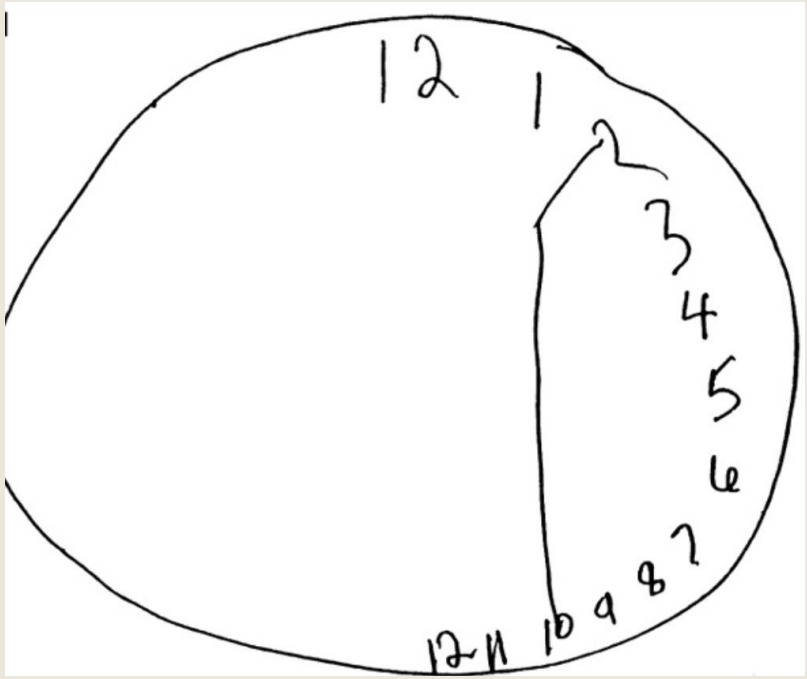
- **PMH:**
  - *HTN*
  - *HLD*
  - *CAD s/p stent*
  - *Prostate CA s/p prostatectomy*
  - *NIDDM*
  - *Meningioma s/p resection in 2010*
- **SHX:**
  - *Married. Retired machinist. Lives w/ wife in a one-story home. 3 grown children*
- **Medications:**
  - *ASA 81 mg daily*
  - *Metoprolol XL 25 mg daily*
  - *Flomax 0.4 mg daily*
  - *Lisinopril 40 mg daily*
  - *Metformin 1000 mg BID*
  - *Crestor 20 mg qHS*
- **FHx:**
  - *Father was an alcoholic*
  - *Mother died of complications of DAT*

Case presentation

- **ROS:** negative
- **Physical Exam:**
  - *BP of 105/70*
  - *Gen: elderly WM who is pleasant and in NAD*
  - *CV: RRR w/ no M/R/G*
  - *Pulm: CTA bilat. No wheezes*
  - *Ab: soft, non-tender, non-distended*
  - *Ext: No C/C/E*
  - *Neuro: AOA x 2.* ***No cogwheeling or tremor evident. Mild stooped posture w/ forward lean***

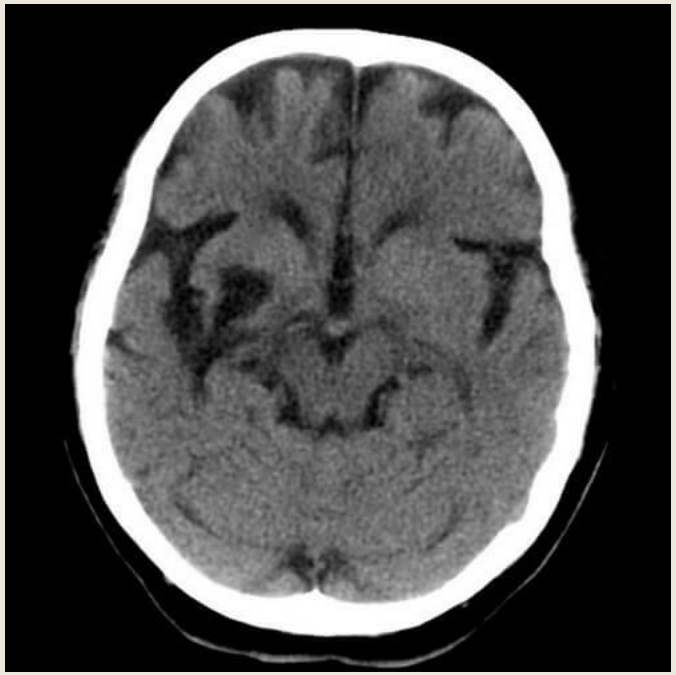
Case Presentation

- **Comprehensive Geriatric Assessment:**
  - *SLUMs: 15/30*
  - *Epworth of 12/24 (frequent daytime sleepiness)*
  - *GDS: 1/15 (+ dropped many interests/activities)*
  - *ADLs: independent*
  - *IADLs: needs assistance w/ cooking, cleaning, finances, driving, laundry, medications*



Case Presentation

- **Lab work significant for:**
  - *HgA1C of 5.7%*
  - *T chol of 120, LDL of 55*
  - *Electrolytes, B12, TSH all WNL*
- **CT head:** Bifrontal and R temporal lobe encephalomalacia w/ mild cerebral atrophy



Case Presentation

- **Assessment/Plan:**
  - *Dx w/ dementia. Did not specify a type in my note at the first visit*
    - Has risk factors for both vascular and Alzheimer's Dementia
  - *D/C Metformin, as HbA1C was low*
  - *Decrease crestor (hx of CAD s/p stent, but LDL is 65)*
  - *F/U for repeat SLUMs in 4 mos*

Case Presentation

- ~6 mos later, hallucinations were occurring daily and were distressing.
  - *Seeing small dwarfs/elves*
  - *Could no longer distinguish between reality and hallucinations*
  - *Unable to go out in public because he was constantly pointing at unseen people and objects.*
  - *Would not sit in certain chairs because people were already sitting there and he was offering food and drinks to unseen people*
- Discussed risks vs benefits of starting an antipsychotic
- Started seroquel 12.5 mg qHS
- After 2 weeks, increased dose to BID

WHAT DO YOU THINK HAPPENED NEXT?

The elves went from this....

To this...

WHAT DID I DO WRONG?

Case Presentation

- Pt likely had Lewy Body Dementia and was extremely sensitive to antipsychotics
- He began to hit the elves with golf clubs in the house, prompting his wife to call me
- Admitted pt acutely to the inpatient geriatric psychiatry unit
- After a several week stay, he was discharged on zyprexa 5 mg BID and namenda 5 mg BID

Case Presentation

- At his first geriatric psych f/u, he was still having hallucinations on zyprexa but was able to state that others could not see them and they were not reality-based
- Did not seem as troubled by them
- Wife felt motor symptoms were more pronounced. More slow gait w/ limited arm movement, taking longer to get dressed, difficulty tying shoes, etc

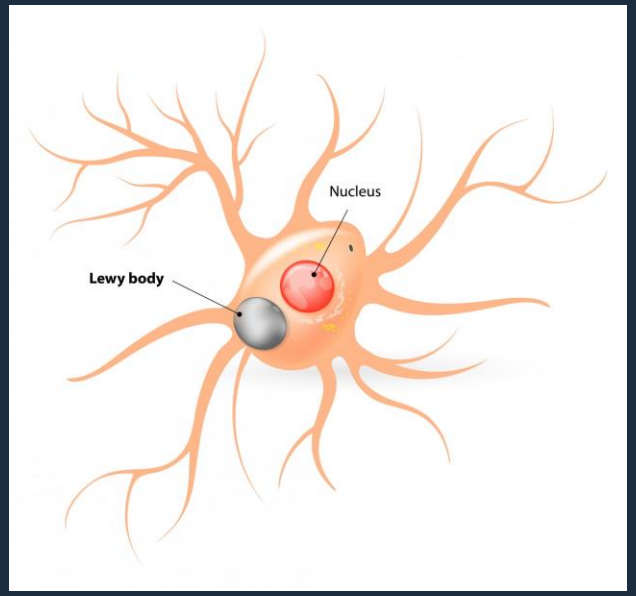
Case Presentation

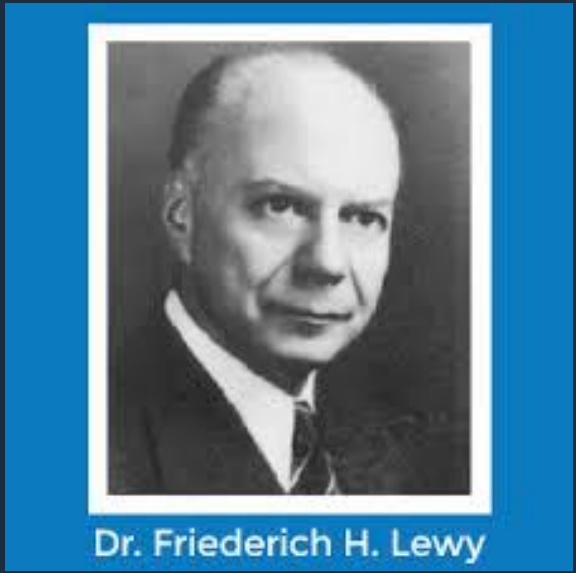
- Neuropsychiatric testing → deficits on all cognitive measures, including visuospatial, learning, recall, verbal fluency, processing speed and problem solving
- Dx → “neurodegenerative” dementia such as Lewy Body Dementia because of the simultaneous onset of cognitive symptoms and visual hallucinations 2 yrs prior w/ more recent onset of mild motor symptoms
- Ultimately, zyprexa was stopped as pt developed increasing Parkinsonian symptoms

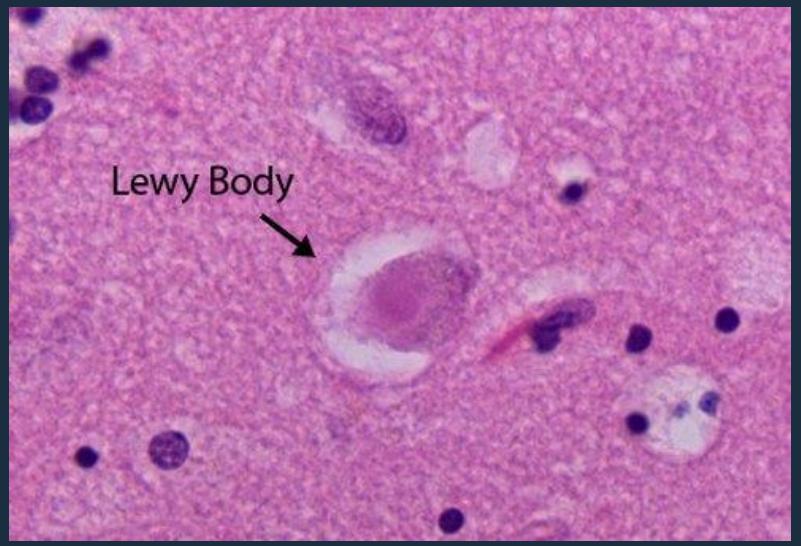
Case Presentation

- Over the next year, both memory and hallucinations fluctuated but w/ overall worsening trajectory
- Tried several medication regimens (Aricept, namenda, zyprexa, zoloft, exelon patch, seroquel again—25 mg TID and 50 mg qHS) w/o improvement
- Started accusing wife of stealing from him, hiding things from him and sleeping with the neighbors
- Was re-admitted to geriatric psychiatry unit with increased agitation. Stopped eating and ambulating and was d/c to NH w/ hospice after one month

NOW ON TO LEWY BODY DEMENTIA...





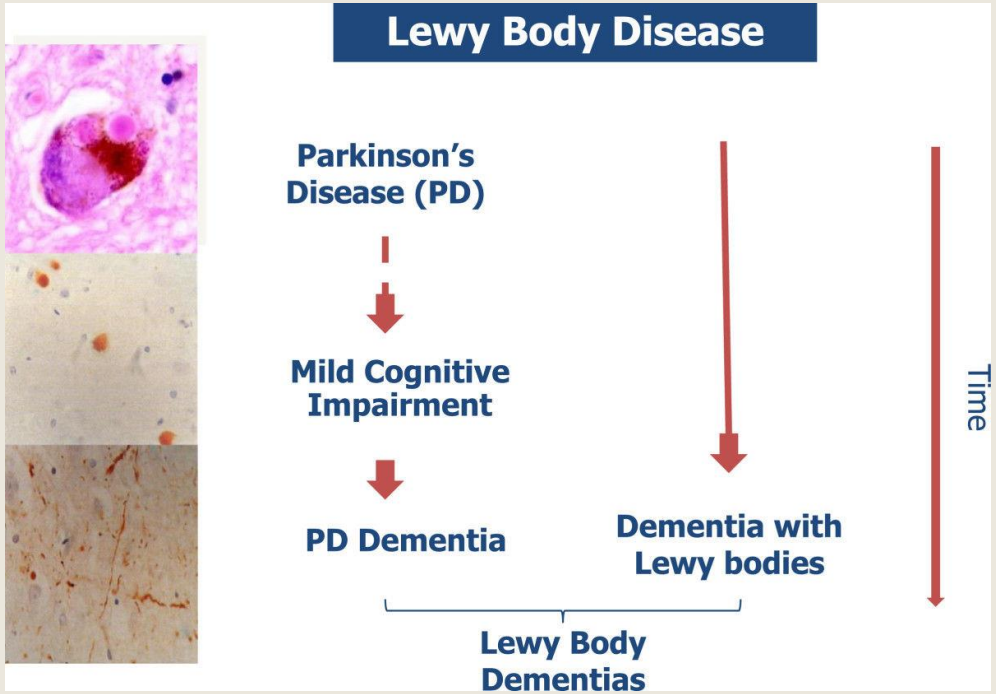


Background

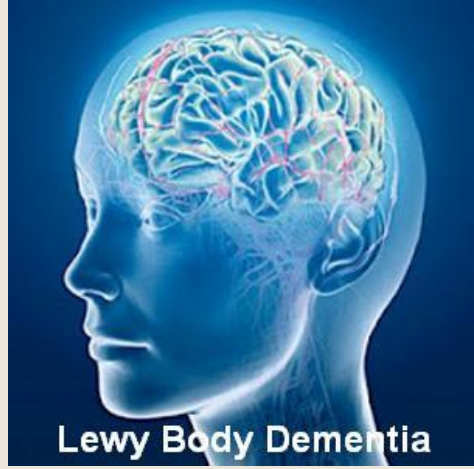
- Lewy Bodies (LB): first discovered in neurons by German Neurologist Dr. Friedrich Lewy in 1912
- LB are formed from aggregation of a protein, ∝-synuclein, in the cytoplasm of neuronal cells
  - *Synucleinopathies include multiple system atrophy, Parkinson's disease, Lewy body dementia*
- Symptoms result from the accumulation of LBs in various parts of the brain and include cognitive and motor deficits affecting mood, behavior, sleep, movement and thinking

Background

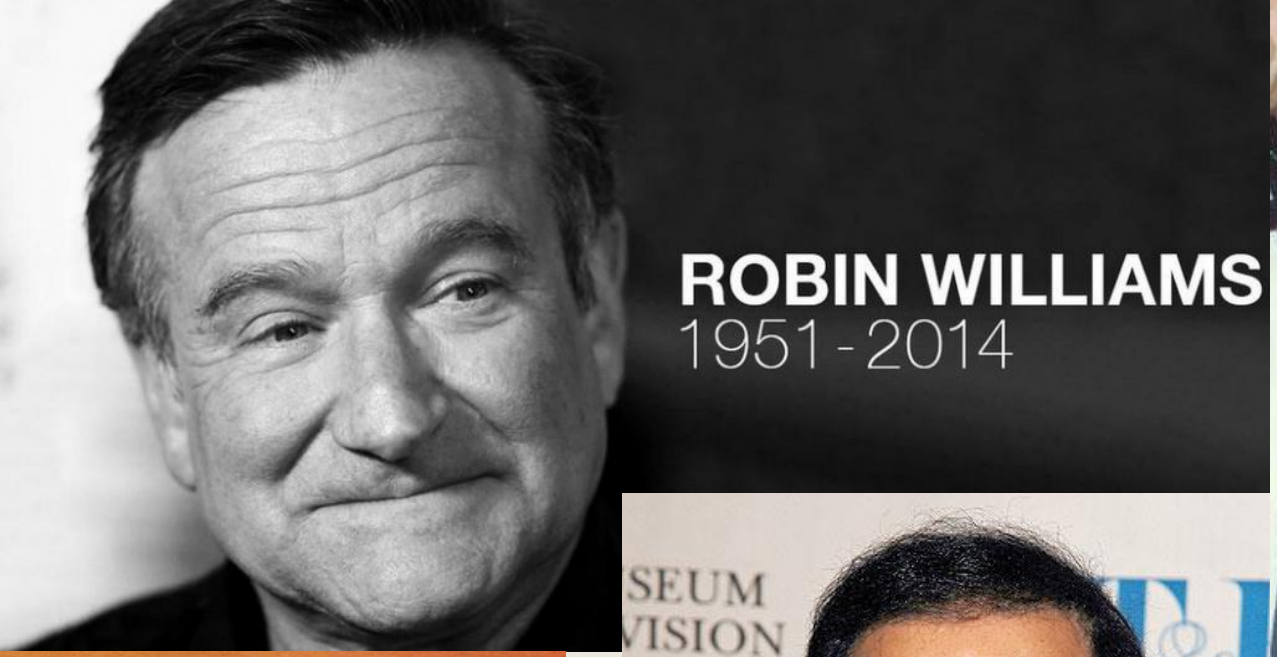
- LBD and Parkinson's Disease with Dementia (PDD):
  - *Many overlapping symptoms*
  - *In later stages of the disease course, can be impossible to distinguish from one another*
- In **PDD, motor symptoms precede cognitive deficits by years**
- In **LBD, cognitive changes appear prior to motor symptoms**, which may not occur until much later in the disease course

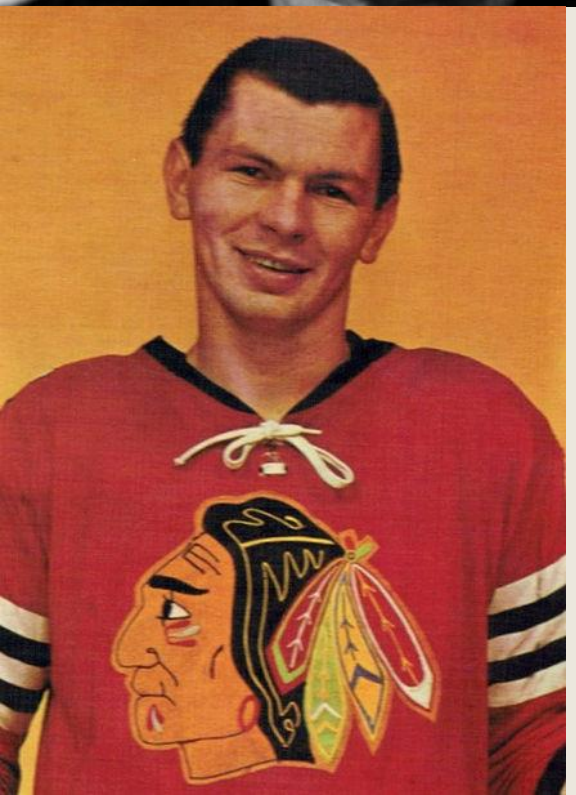


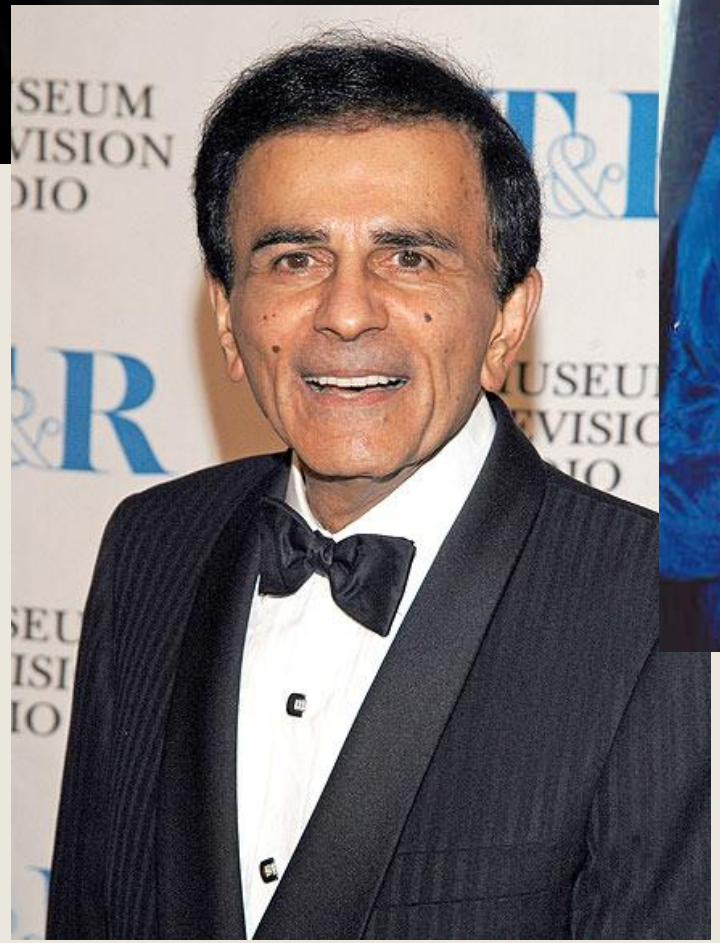
Epidemiology

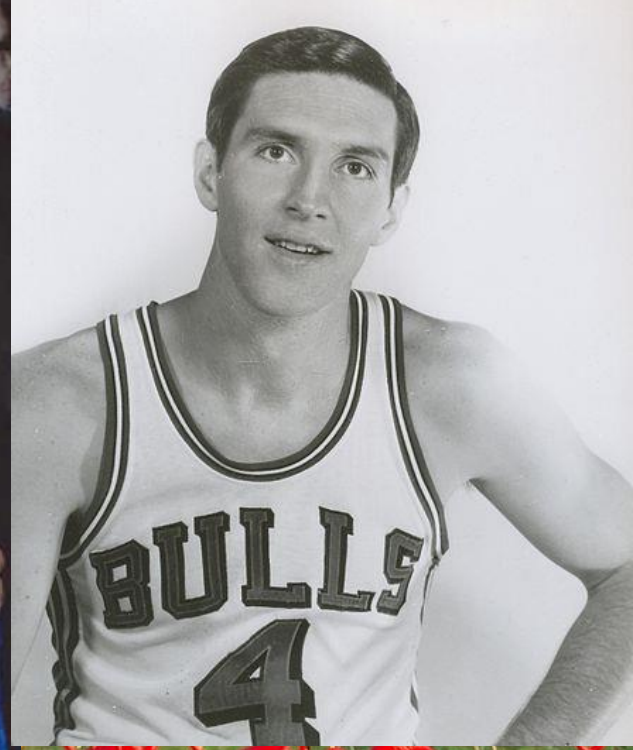


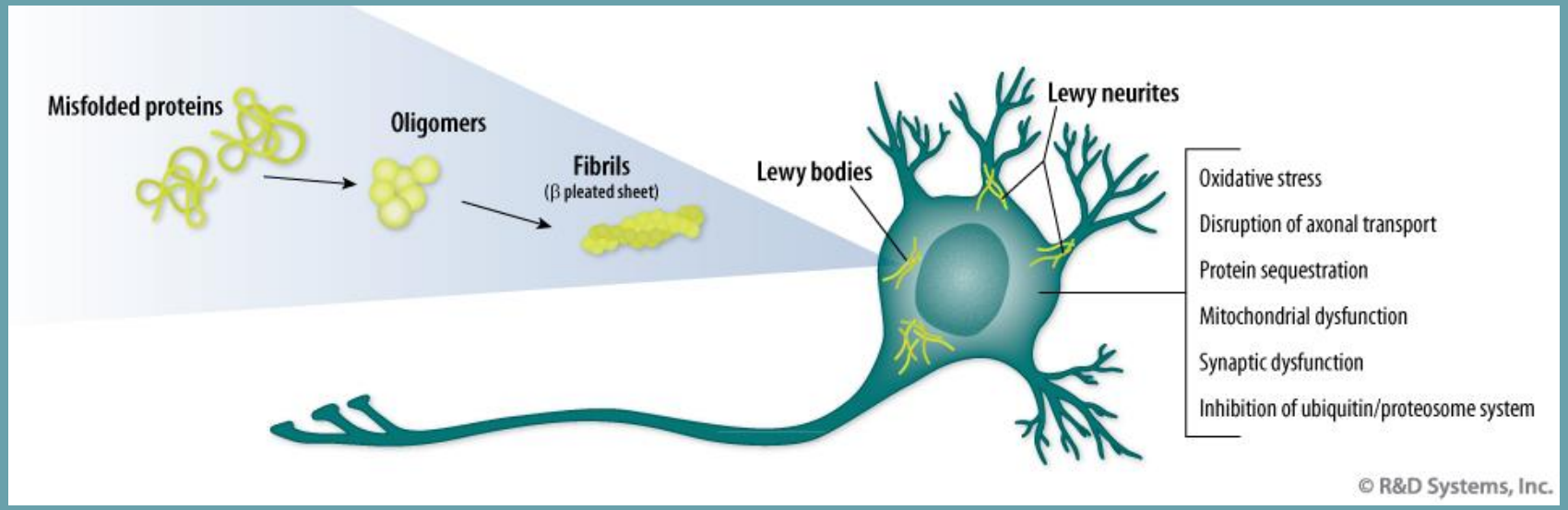
- LBD affects an estimated 1.4 million Americans
- 2nd most common neurodegenerative dementia in those >65 y/o following Alzheimer's Disease
  - *Represents ~10-20% of dementia cases (20-25% of autopsy cases)*
- Biggest risk factor is age
  - *Onset is typically 70-85 yrs of age*
- More common in men
- Death typically occurs 5-7 yrs after onset


ROBIN WILLIAMS
1951 - 2014

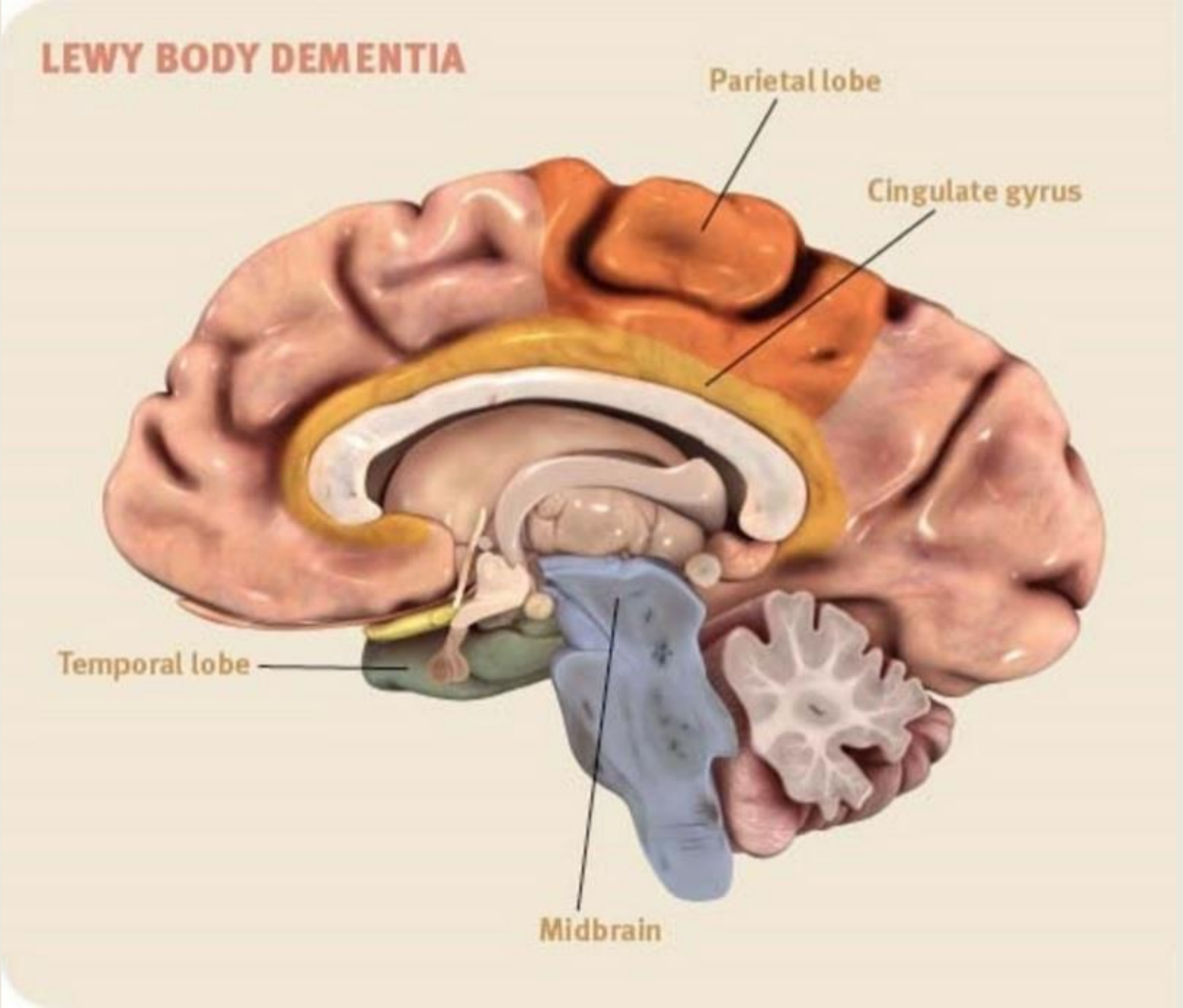


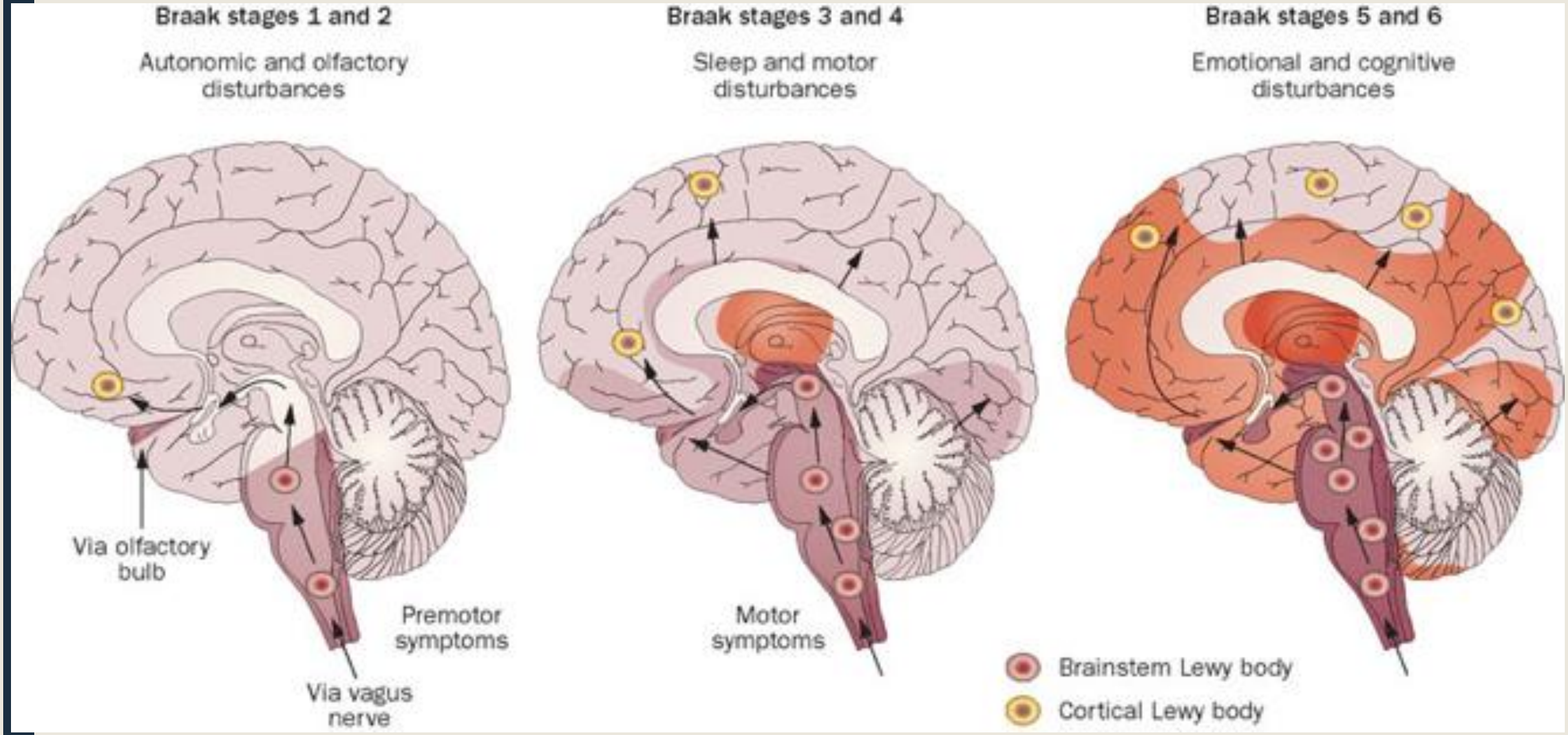



BULLS
4



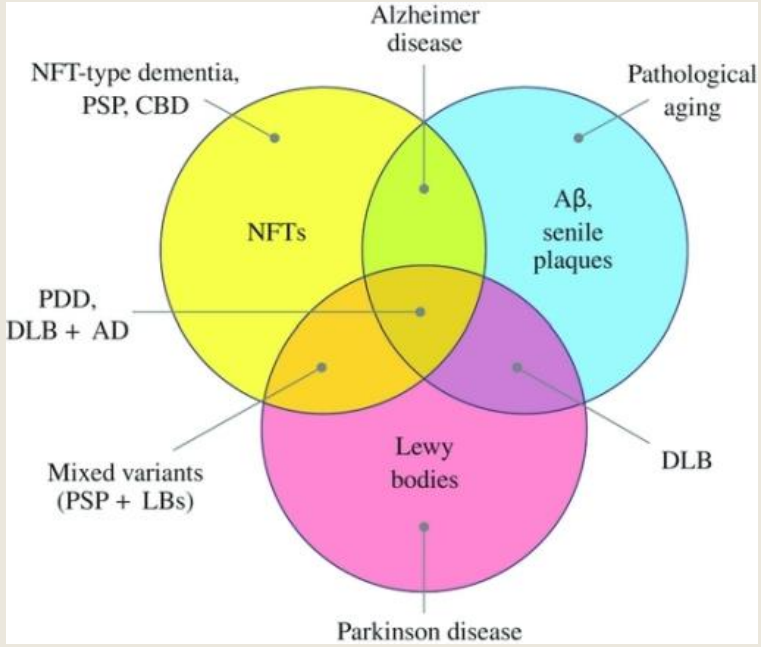
PATHOPHYSIOLOGY


LEWY BODY DEMENTIA
Parietal lobe
Cingulate gyrus
Temporal lobe
Midbrain



Doty RL. Olfactory dysfucntion in parkinson disease. Nat Rev Neurol 2012;8(6):329-39.

Pathophysiology



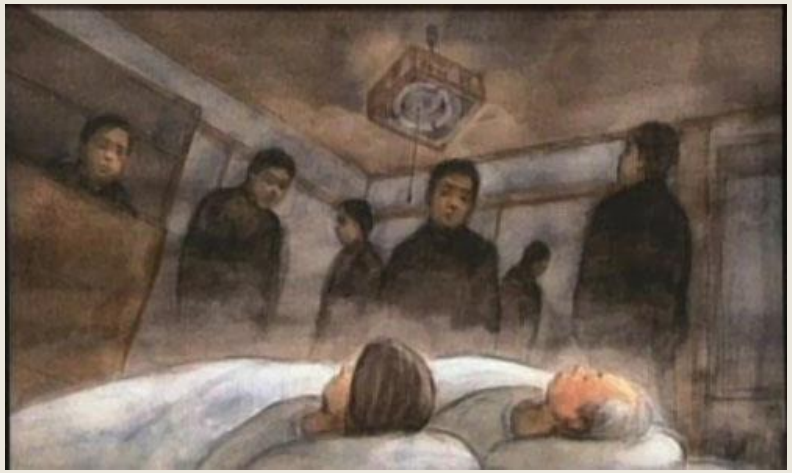
- **There is overlap between all types of dementia**
  - *Increased number of amyloid-beta plaques in addition to LBs*
  - *Neurofibrillary tangles may also occur*
  - *When ∝-synuclein deposits in AChE-rich neuronal areas, AChE deficiencies occur, mimicking DAT*
  - *Frequently, will have findings of vascular dementia in brain as well*

Clinical Presentation

- **Most common presenting symptoms:**
  - *Loss of executive function w/ impaired planning, delayed processing of information*
  - ***Visuospatial deficits***
  - *Memory impairment*
  - ***Fluctuation in alertness, cognition, and attention***
  - ***Visual hallucinations/Illusions***
  - ***Sleep disorders***
  - *Behavioral and mood symptoms → MDD, apathy, GAD, delusions, paranoia, agitation*
  - *Changes in autonomic function → orthostatic hypoTN, temperature regulation, bowel/bladder incontinence*
  - ***Parkinsonian motor signs***

Lewy Body Dementia Association. https://www.lbda.org. Accessed Dec. 26, 2017

Galasko D. Lewy Body Disorders. Neurol Clin 2017:325-38.



Schapira A, Chaudhuri K, Jenner P. Non-motor features of Parkinson Disease. Nat Rev Neurosci 2017’18(8):435-50.

Clinical Presentation

- **Hallucinations in LBD:**
  - *Very characteristic of LBD*
    - Secondary to high burden of LBs in temporal, occipital lobes + cholinergic and dopaminergic deficits in multiple areas of the brain
  - *Usually have recurrent, complex, detailed hallucinations*
  - *May misinterpret shadows/objects → illusions*
  - *May develop delusions regarding the hallucinations and illusions*
  - *Occur in 80% of LBD pts and in 30% of PD pts*

Clinical Presentation

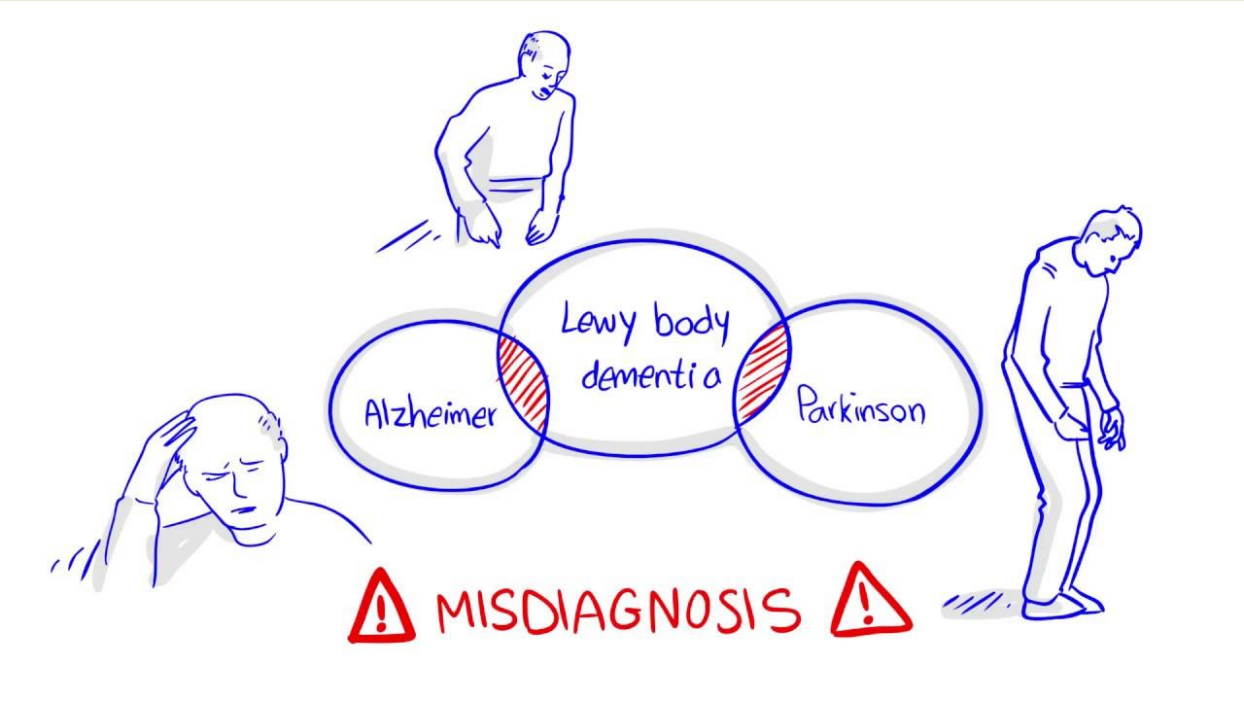
- **Parkinsonian motor symptoms:**
  - *Rest tremor, stooped posture, gait slowing, postural instability*
  - *Rest tremor is often less common in LBD than in PDD, whereas the axial signs are more prominent*
  - *Occur in >85% of pts*
- **REM sleep behavioral d/o (RBD):**
  - *Occurs frequently in LBD, PD and multisystem atrophy and may precede dx by years*
  - *∝-synuclein often first deposits in RAS and then spreads to other areas over course of yrs*
  - *Lack of motor inhibition in REM sleep and manifests w/ pts shouting, kicking, thrashing, punching (acting out dreams) during sleep*
  - *Occurs in ~75% of pts*

Galasko D. Lewy Body Disorders. Neurol Clin 2017:325-38.

Diagnosis

- **There is often a delay in making the diagnosis**
  - *Commonly misdiagnosed as late onset psychiatric d/o*
  - ***Average pt sees 3-4 drs prior to dx made!!***
- It is important to make an accurate dx because many medications used for other forms of dementia make symptoms of LBD worse → antipsychotics
- Diagnosis is based on clinical hx, physical exam, cognitive testing and imaging
- Although there are many genetic factors/gene mutations that may lead to LBD, there is no current role for clinical genetic testing outside of research

Diagnostic Criteria for LBD



- **Major clinical conundrum is differentiating LBD vs PDD vs DAT**
- In 2005, diagnostic guidelines for LBD and PDD were updated and arbitrary **"1-year rule" proposed**:
  - *PDD → motor symptoms precede cognitive decline by >1 year*
  - *LBD → cognitive decline precedes or accompanies the first motor symptoms*

McKeith I, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy Bodies (DLB). Neurology 1996;67:1113-24.

Diagnostic Criteria for LBD

Table 2

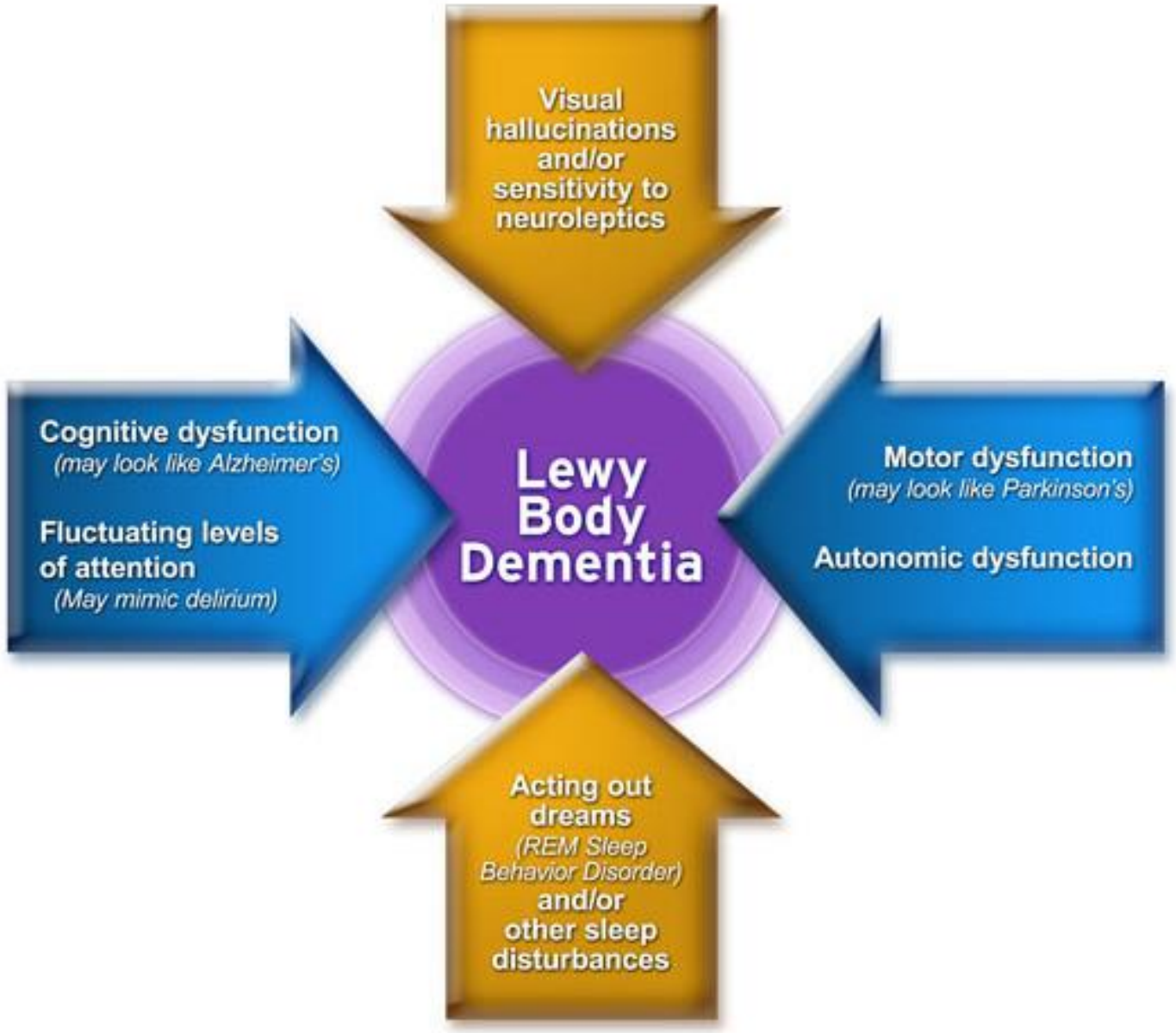
Frequency of core diagnostic features in the patients with DLB

Clinical feature	Frequency
Parkinsonism	68/72 (94.4%)
REM sleep behavior disorder	55/72 (76.4%)
Visual Hallucinations	45/72 (62.5%)
Fluctuations	33/72 (45.8%)

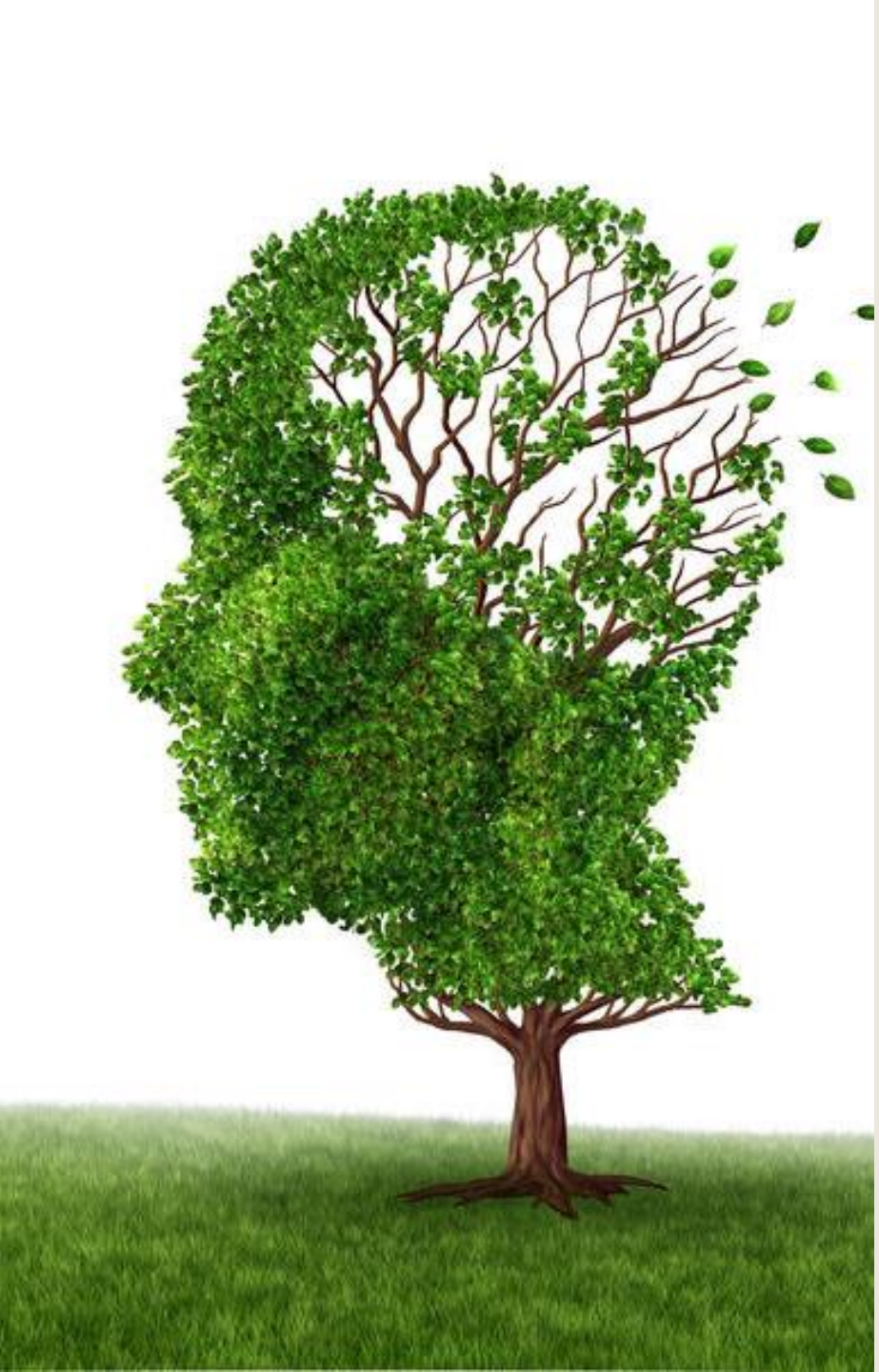
REM = Rapid Eye Movement

- Dx requires dementia + 2 or more of following:
  - *Fluctuating cognition*
  - *Visual hallucinations*
  - *Parkinsonism*
  - *REM sleep behavioral d/o*

Whitwell J, Weigand S, Shiung M, et al. Focal atrophy in Dementia with Lewy Bodies on MRI: a distinct pattern from Alzhemier's disease. Brain 2007;130(Pt 3):708-19.



https://www.lbda.org/content/lbd-spectrum. Accessed January 1, 2018



Diagnostic Criteria for LBD

- **“Supportive” Features include:**
  - *Neuroleptic sensitivity*
  - *Autonomic dysfunction:*
    - Orthostatic hypoTN
    - Syncope
    - Constipation
    - Urinary incontinence
  - *Recurrent falls*
  - *Depression/anxiety*
  - *Delusions*
  - *Anosmia*

Diagnosis—Imaging

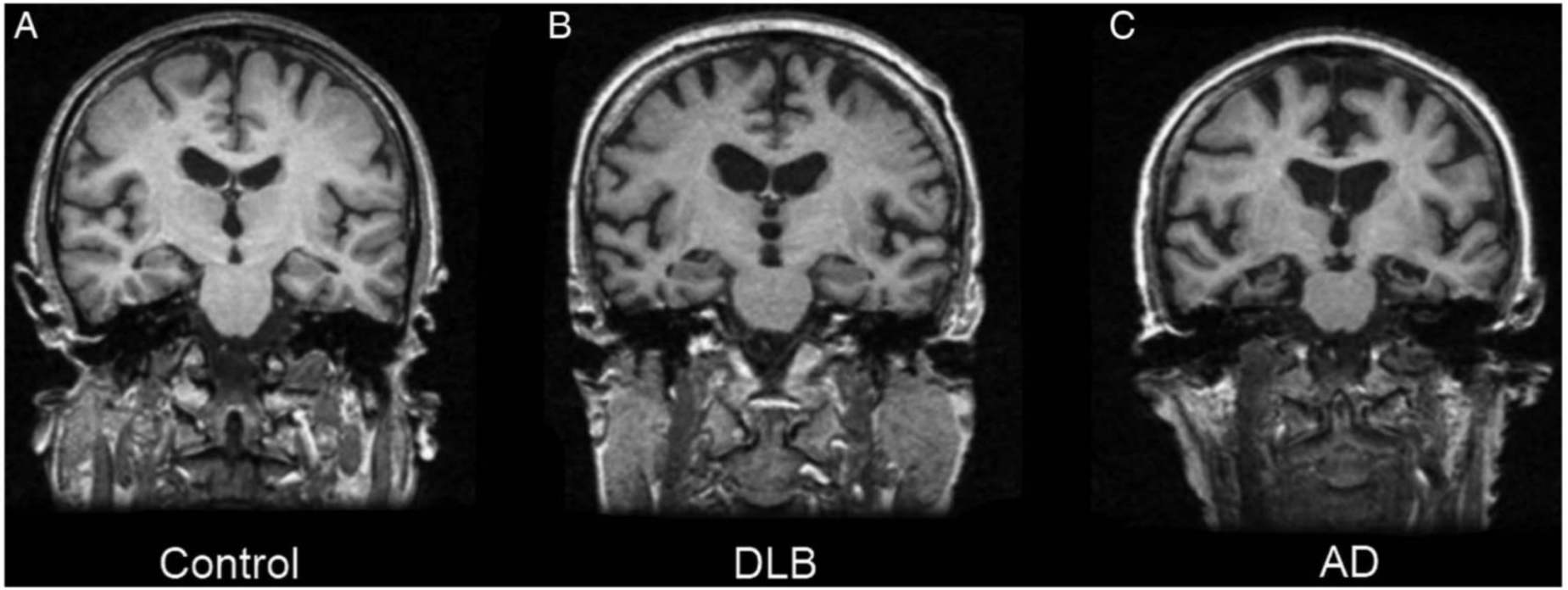
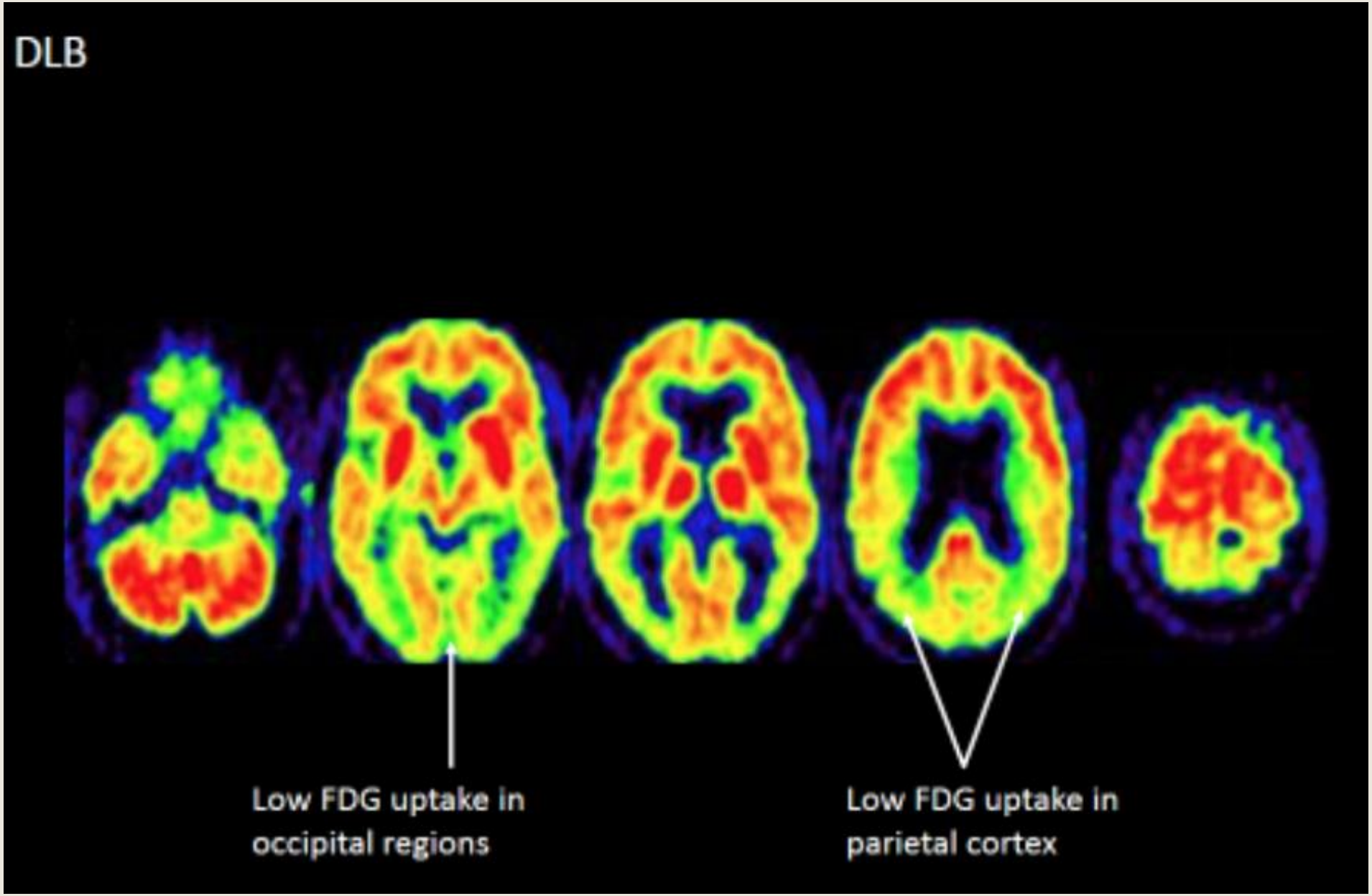
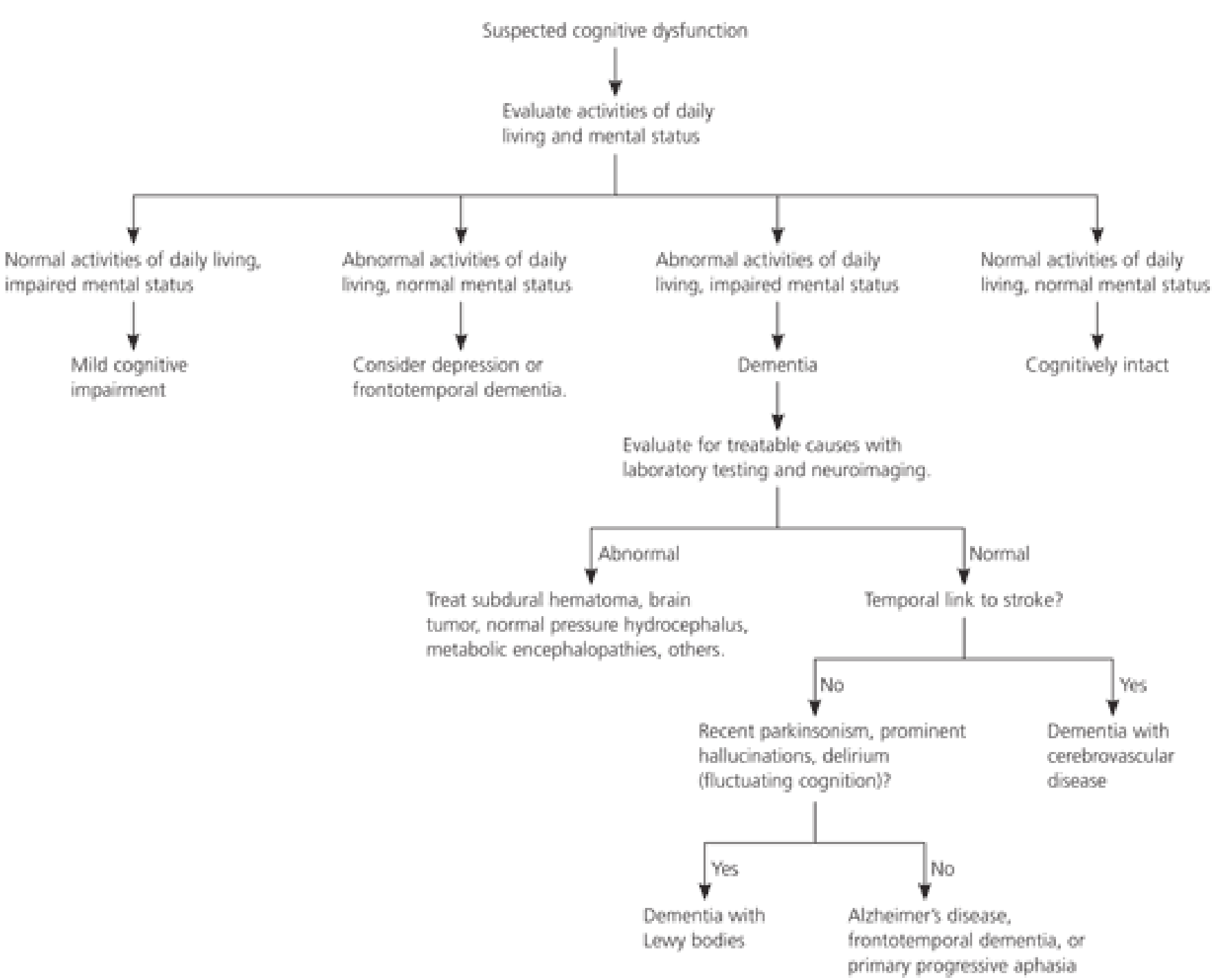


Figure 1 Coronal view of a structural MRI brain scan in (A) Control, (B) Dementia with Lewy bodies (DLB) and (C) AD. Note the relatively preserved medial temporal lobes in DLB compared with AD.

Gore R, Vardy E, O'Brien J. Delirium and dementia with Lewy bodies: distinct diagnoses or part of the same spectrum? J Neurol Neurosurg Psychiatry 2015;86:50-9.


DLB
Low FDG uptake in occipital regions
Low FDG uptake in parietal cortex



Neef D, Walling A. Dementia with Lewy Bodies: an emerging disease. Am Fam Physician 2006;73(7):1223-29.

LBDA
LEWY BODY DEMENTIA ASSOCIATION

EARLY DIFFERENTIATING SYMPTOMS

	LBD	Alzheimer's	Parkinson's
Decline in thinking abilities that interferes with everyday life	Always	Always	Possible years after diagnosis
Significant memory loss	Possible	Always	Possible years after diagnosis
Planning or problem-solving abilities	Likely	Possible	Possible
Difficulty with sense of direction or spatial relationships between objects	Likely	Possible	Possible
Language problems	Possible	Possible	Possible
Fluctuating cognitive abilities, attention or alertness	Likely	Possible	Possible
Changes in mood	Possible	Possible	Possible
Hallucinations	Possible	Unlikely	Possible
Severe sensitivity to medications used to treat hallucinations	Likely	Unlikely	Possible
Changes in walking or movement, such as slower, smaller steps, problems using hands, tremors	Possible	Unlikely	Always
Balance problems and/or falls	Possible	Unlikely	Possible
Rapid eye movement (REM) sleep behavior disorder	Possible	Unlikely	Possible

WE'RE HERE TO HELP

Visit the LBDA website at lbda.org to learn more about LBD, find resources to get the help you need, and connect with the LBDA community.

Treatment

- There is **no high-level evidence to support any forms of treatment.** Only a few studies with small numbers of participants have been done
- **Medication choices should target symptoms**
- **Atypical antipsychotics may improve hallucinations, but many patients do not tolerate them**
  - *Mild, non-threatening hallucinations should not be tx pharmacologically*
  - *Often worsen movement symptoms of Parkinson's because of effects on dopamine*
- **Pimavanserin (Nuplazid):**
  - *First FDA approved medication for the treatment of hallucinations/psychosis in PD and is often used in those w/ LBD because of the similarity between PDD and LBD*
  - *2nd generation anti-psychotic*
  - *Less side effects in those with PD/LBD in comparison to other anti-psychotics because it does not affect dopamine levels*

Treatment

- **Acetylcholinesterase inhibitors (AChEI) may improve cognition**
  - *Some evidence that LBD pts have a greater response to AChEI than DAT pts*
  - *In some studies, AChEI help w/ hallucinations*
- **SSRIs may help depression and apathy**
- **Carbidopa/Levidopa may improve motor symptoms**
  - *Use caution because this can worsen hallucinations*
  - *Clinical response to carbidopa/levidopa is often less dramatic in LBD than in PD*

McKeith I, Del-Ser T, Spano PF, et al. Efficacy of rivastigmine in dementia with Lewy Bodies: a randonmized, double-blind, placebo-controlled international study. Lancet 2000;356:2031-6.

Treatment

- **Important medication principles:**
  - *Multiple meds may be needed to control symptoms, i.e., AChEI for cognition, SSRI for depression/apathy, sinemet for motor symptoms and antipsychotic for hallucinations*
    - Caution w/ drug-drug interactions and unwanted side effects
    - Use lowest dose and titrate upwards
    - Make changes to one med at a time
    - D/C if not effective after a reasonable trial

Exercise and Dementia

- **Exercise has been shown to improve quality of life for all stages of Dementia**
- It likely **works better than our best medications** in improving symptoms and behavioral issues
  - *Can reduce risk of stroke and improve high blood pressure, diabetes, and cholesterol, all of which are risk factors for vascular dementia*
  - *Improved physical fitness can allow for longer independence*
  - *Reduces risk of falls*
  - *Improves mood*
  - *Improves sleep*

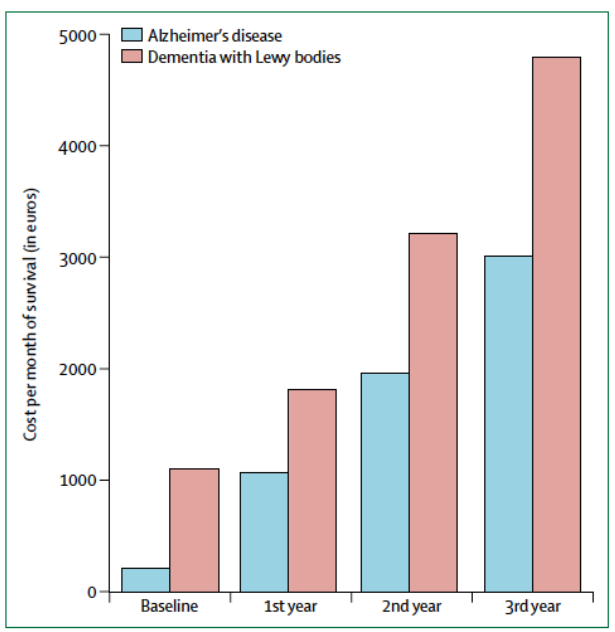


***Figure 3*: Mean costs of care per month of survival from dementia diagnosis for patients with Alzheimer's disease and dementia with Lewy bodies**
Reproduced with permission from Vossius and colleagues.[78]

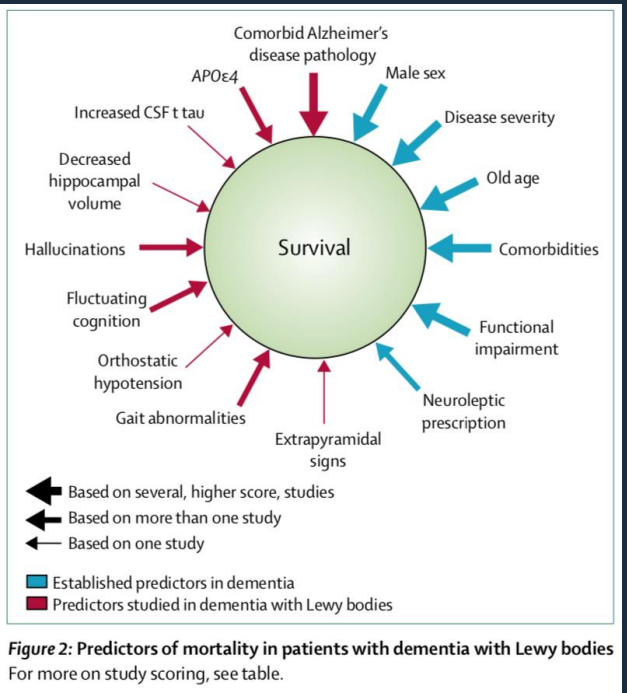


***Figure 2*: Predictors of mortality in patients with dementia with Lewy bodies**
For more on study scoring, see table.

Prognosis

- Lifespan from onset to death is ~5-7 years
- Pt w/ LBD have increased rates of NH placement earlier on in dz course when compared to pts w/ DAT (median time from dz to NH was 1.8 yrs)
- Associated with high levels of caregiver burden and decreased QOL
- Also associated with higher healthcare costs than DAT

Rongve A, Vossius C, Nore S, et al. Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. Int J Geriatr Psychaitry 2014;29:392-98.

Mueller C, Ballard C, Corbett A, et al. The prognosis of dementia with Lewy bodies. Lancet Neurol 2017;16:390-98.

Vossius C, Rongve A, Testad I, et al. The use and costs of formal are in newly diagnosed dementia: a three-year prospective follow-up sstudy. Am J Geriatr Psychiatry 2014;22:381-88.

Summary

- Lewy Body Dementia encompasses both Dementia with Lewy Bodies and Parkinson's Disease with Dementia
- Differentiating between DLB and PDD is difficult and based on an arbitrary "1-year" rule regarding what occurred first—motor symptoms or cognitive symptoms
- DLB is often under and misdiagnosed
- In later stages, DLB, PDD, and DAT are clinically very similar and anatomical studies of the brain reveal overlapping pathology
- There are no evidence-based treatments for the symptoms in DLB and many patients do not tolerate medications

THANKS!

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