Lewy body spectrum disorders: Dementia with Lewy bodies and Parkinson's disease dementia

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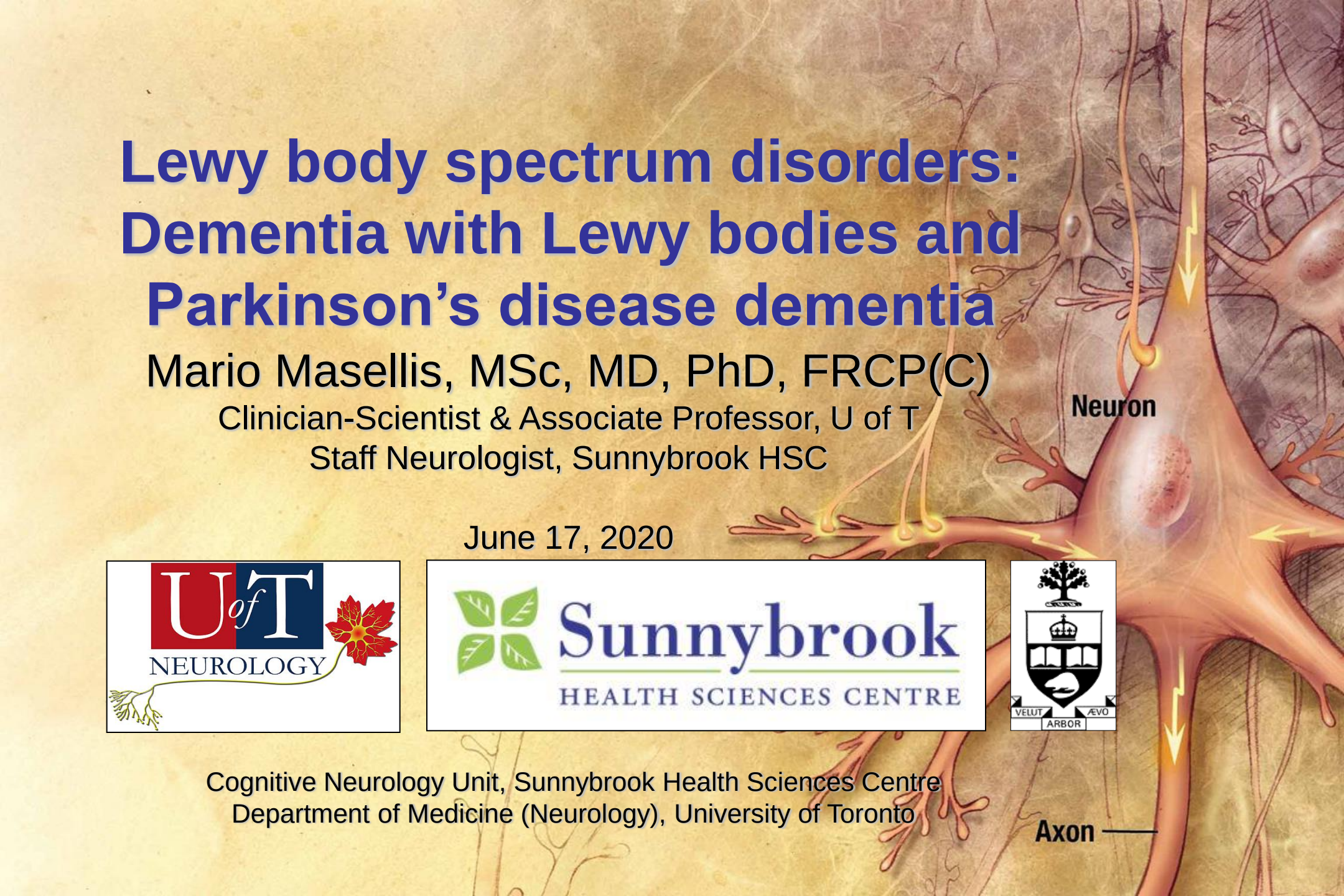


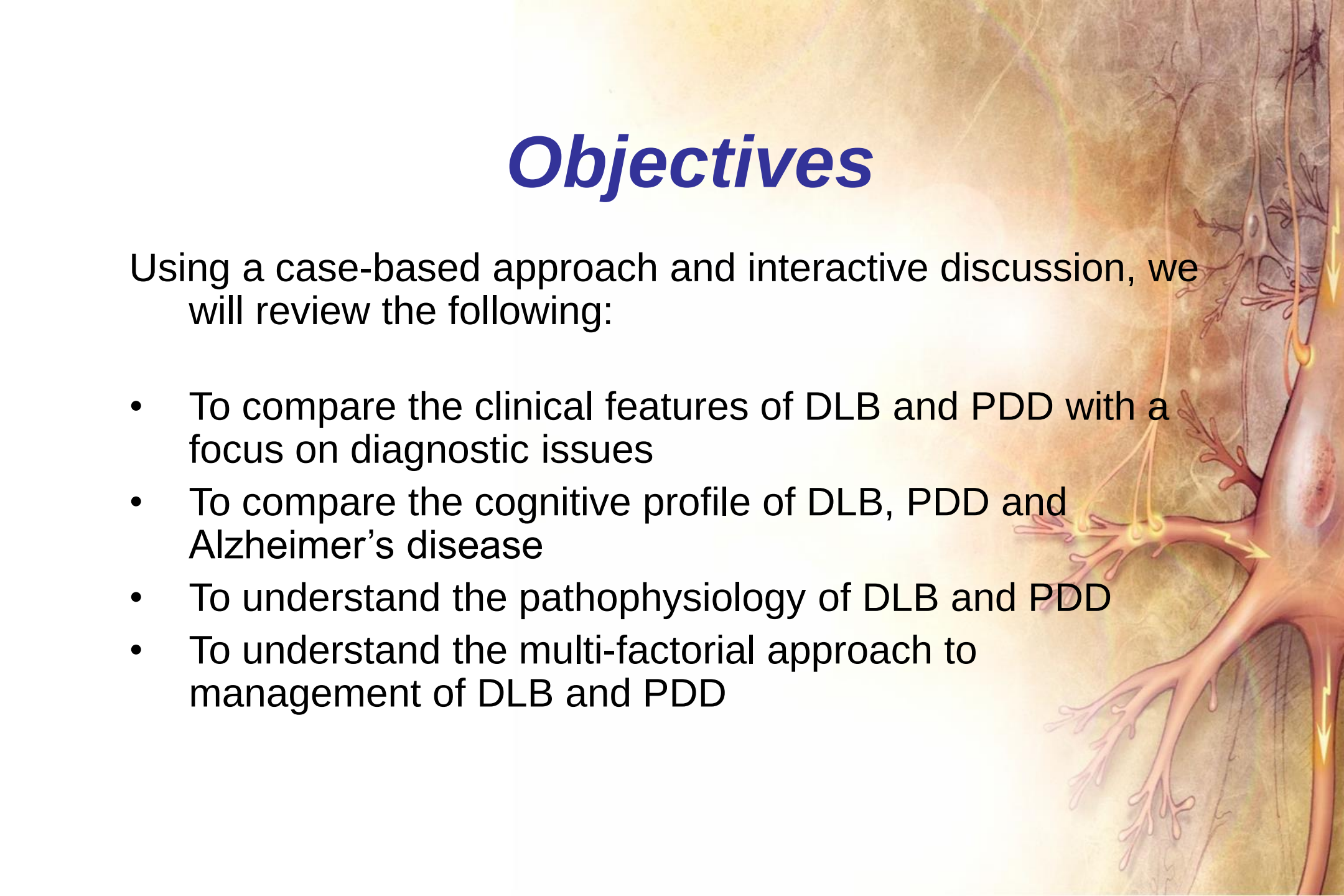
Disclosure of potential conflicts of interest

- Research support, Parkinson Society Canada, Canadian Institutes of Health Research, Ministry of Economic Development and Innovation, Teva, C5R
- Novartis clinical trial, Principal Investigator
- CME Lecturer, Novartis & EMD Serono
- Consultant, Bioscape Medical Imaging CRO

Objectives

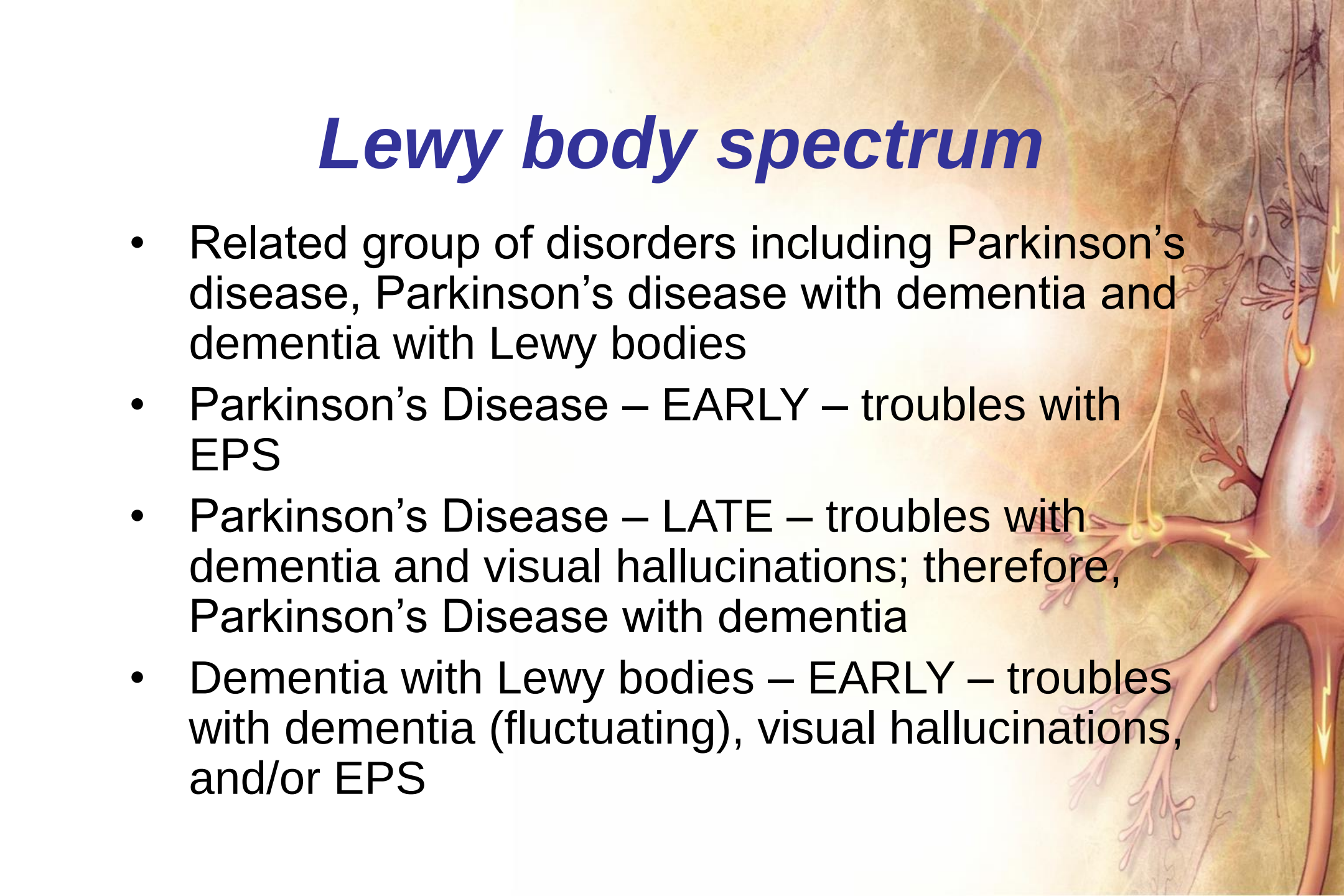
Using a case-based approach and interactive discussion, we will review the following:

- To compare the clinical features of DLB and PDD with a focus on diagnostic issues
- To compare the cognitive profile of DLB, PDD and Alzheimer's disease
- To understand the pathophysiology of DLB and PDD
- To understand the multi-factorial approach to management of DLB and PDD

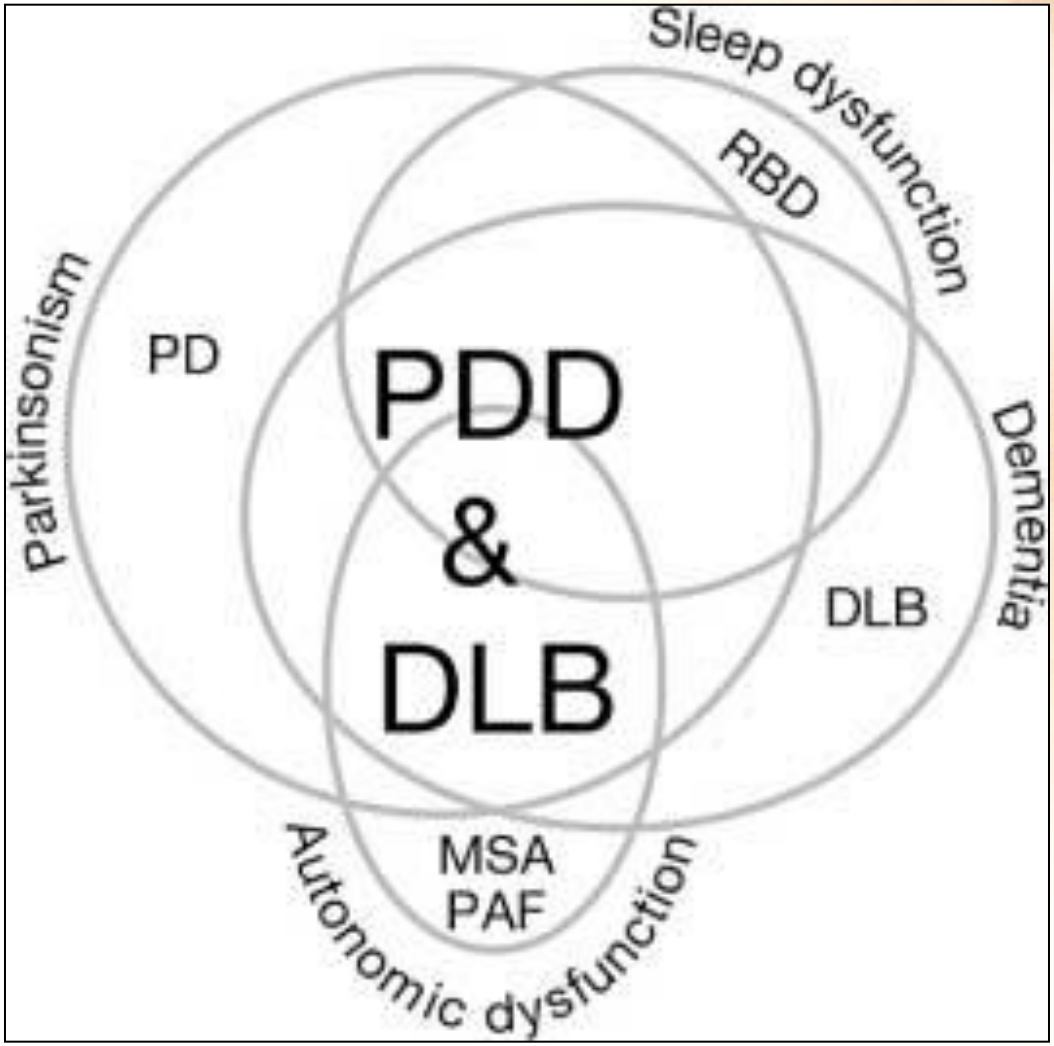


Lewy body spectrum

- Related group of disorders including Parkinson's disease, Parkinson's disease with dementia and dementia with Lewy bodies
- Parkinson's Disease – EARLY – troubles with EPS
- Parkinson's Disease – LATE – troubles with dementia and visual hallucinations; therefore, Parkinson's Disease with dementia
- Dementia with Lewy bodies – EARLY – troubles with dementia (fluctuating), visual hallucinations, and/or EPS

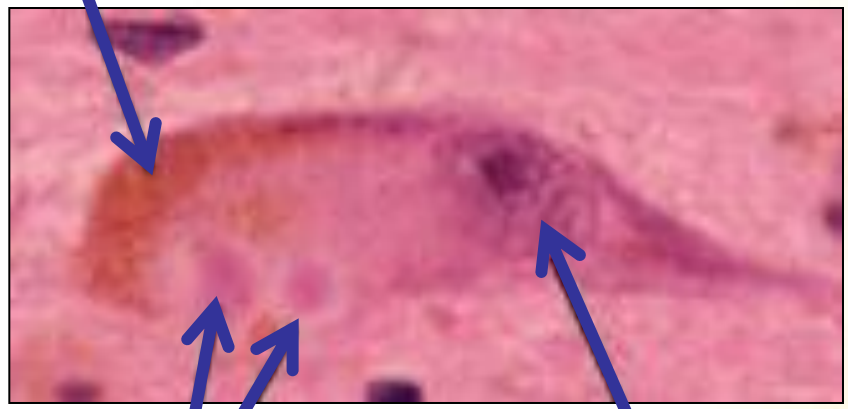


Spectrum of Lewy Body Disease



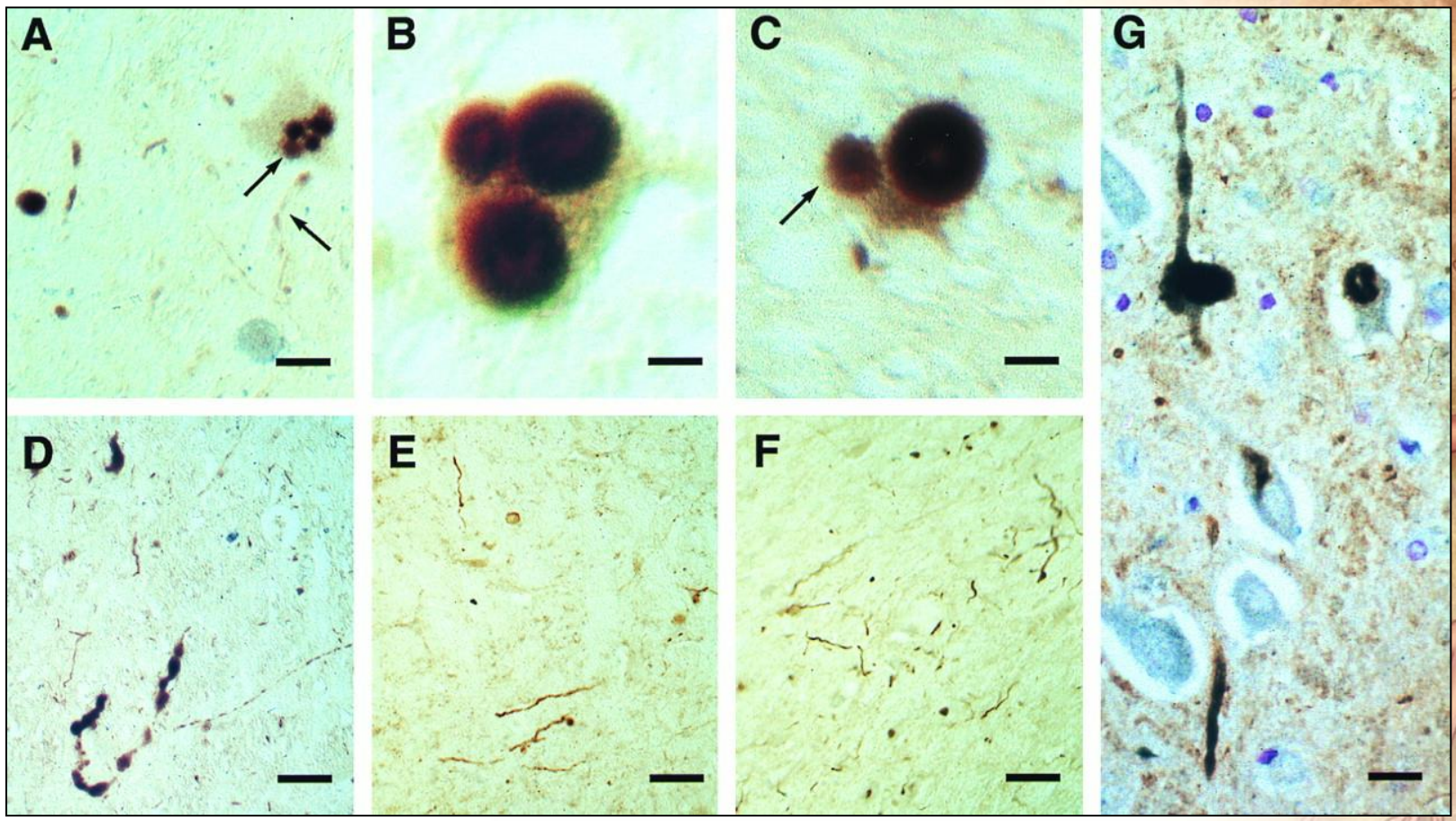
Duda, 2004

PDD and DLB: Common Lewy Body Pathology



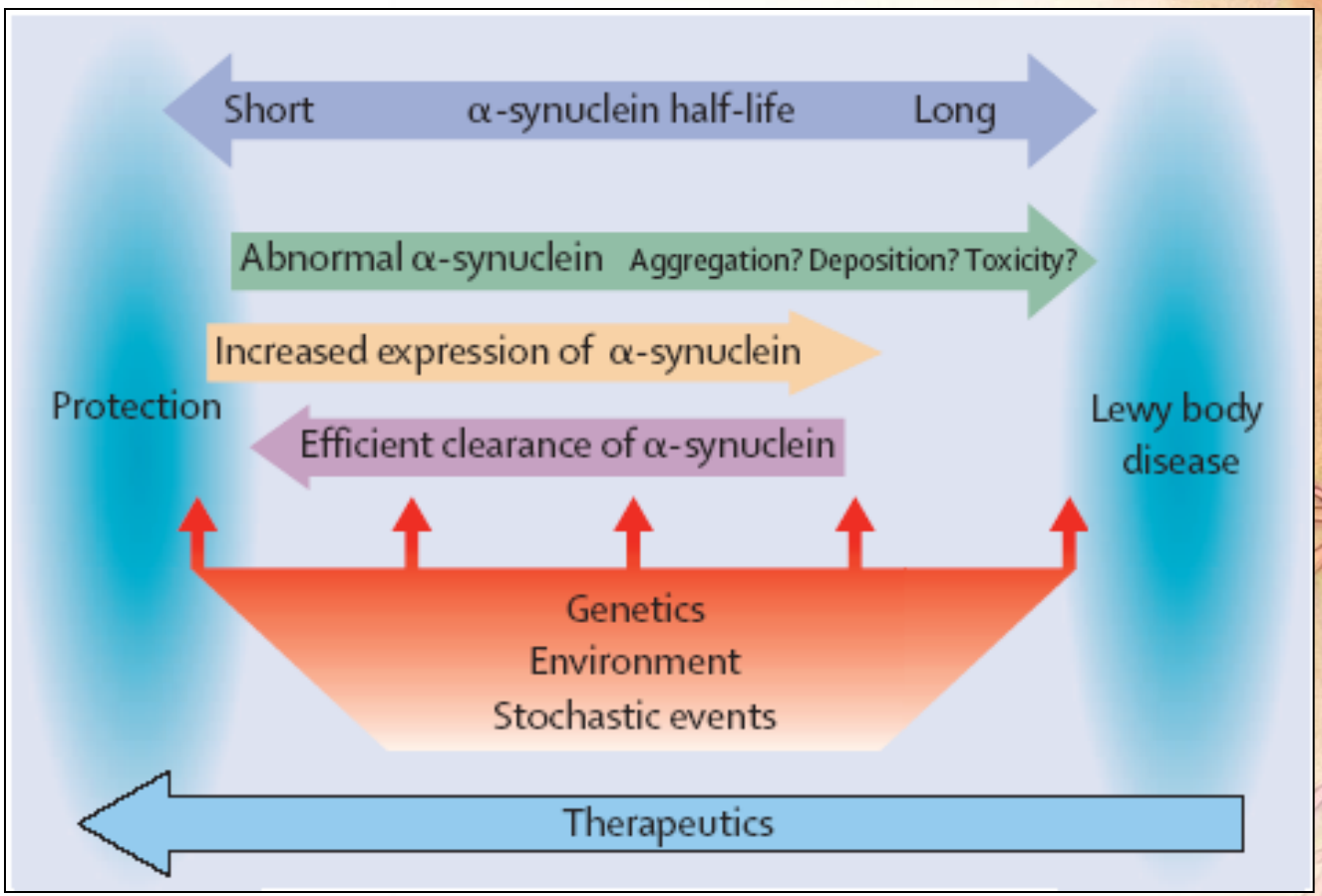
Esiri MM, McShane RH. *Cambridge University Press* 1997
Gelb DJ. *Arch Neurol* 1999;56:33–9

Aggregates of α-synuclein are the major constituent of Lewy Bodies and Neurites

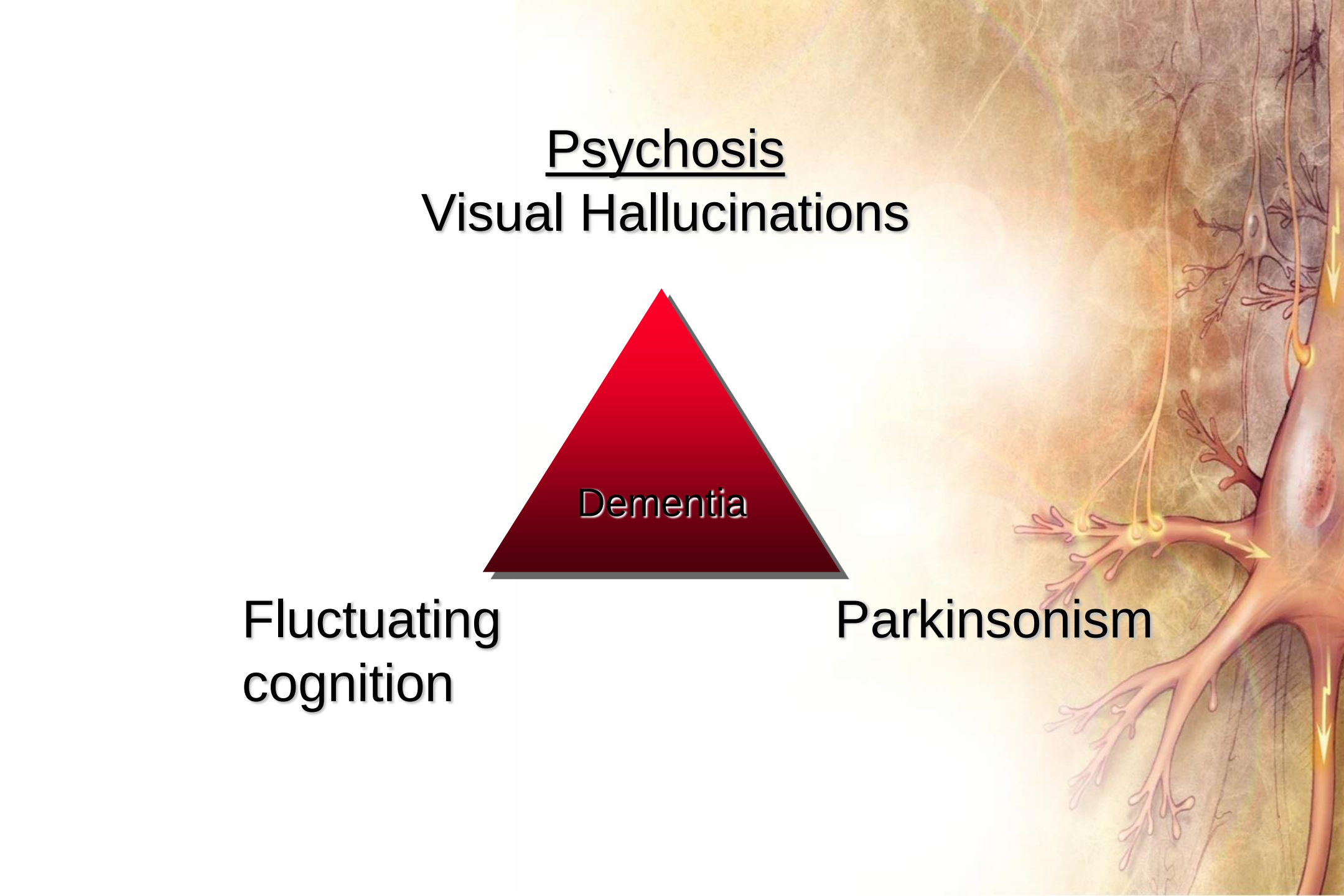


Spillantini et al., 1998

Lewy body spectrum disorders: α-synuclein is the common link



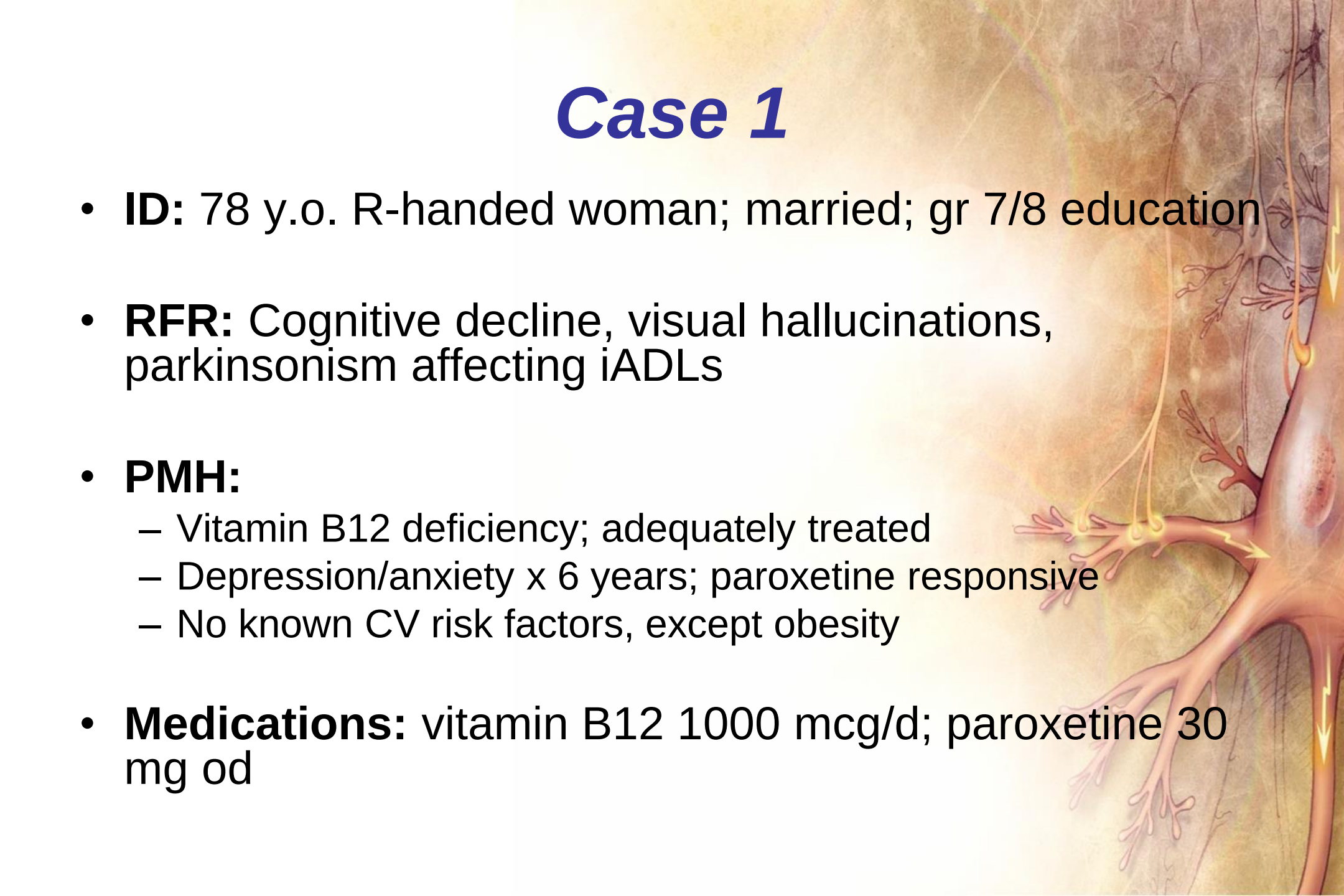
Singleton & Gwinn-Hardy, 2004


Psychosis
Visual Hallucinations
Dementia
Fluctuating cognition
Parkinsonism

Case 1

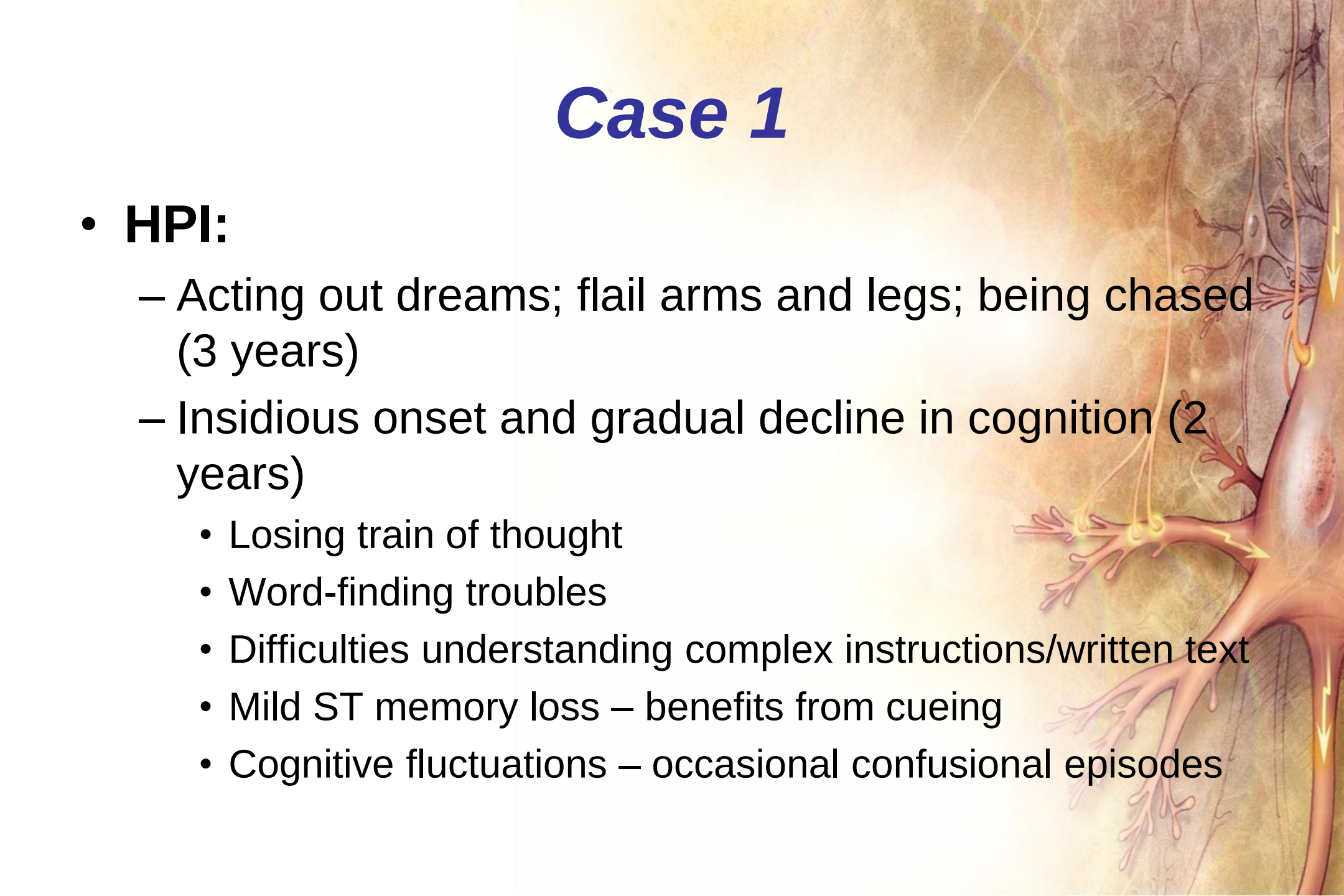
Case 1

- **ID:** 78 y.o. R-handed woman; married; gr 7/8 education
- **RFR:** Cognitive decline, visual hallucinations, parkinsonism affecting iADLs
- **PMH:**
  - Vitamin B12 deficiency; adequately treated
  - Depression/anxiety x 6 years; paroxetine responsive
  - No known CV risk factors, except obesity
- **Medications:** vitamin B12 1000 mcg/d; paroxetine 30 mg od



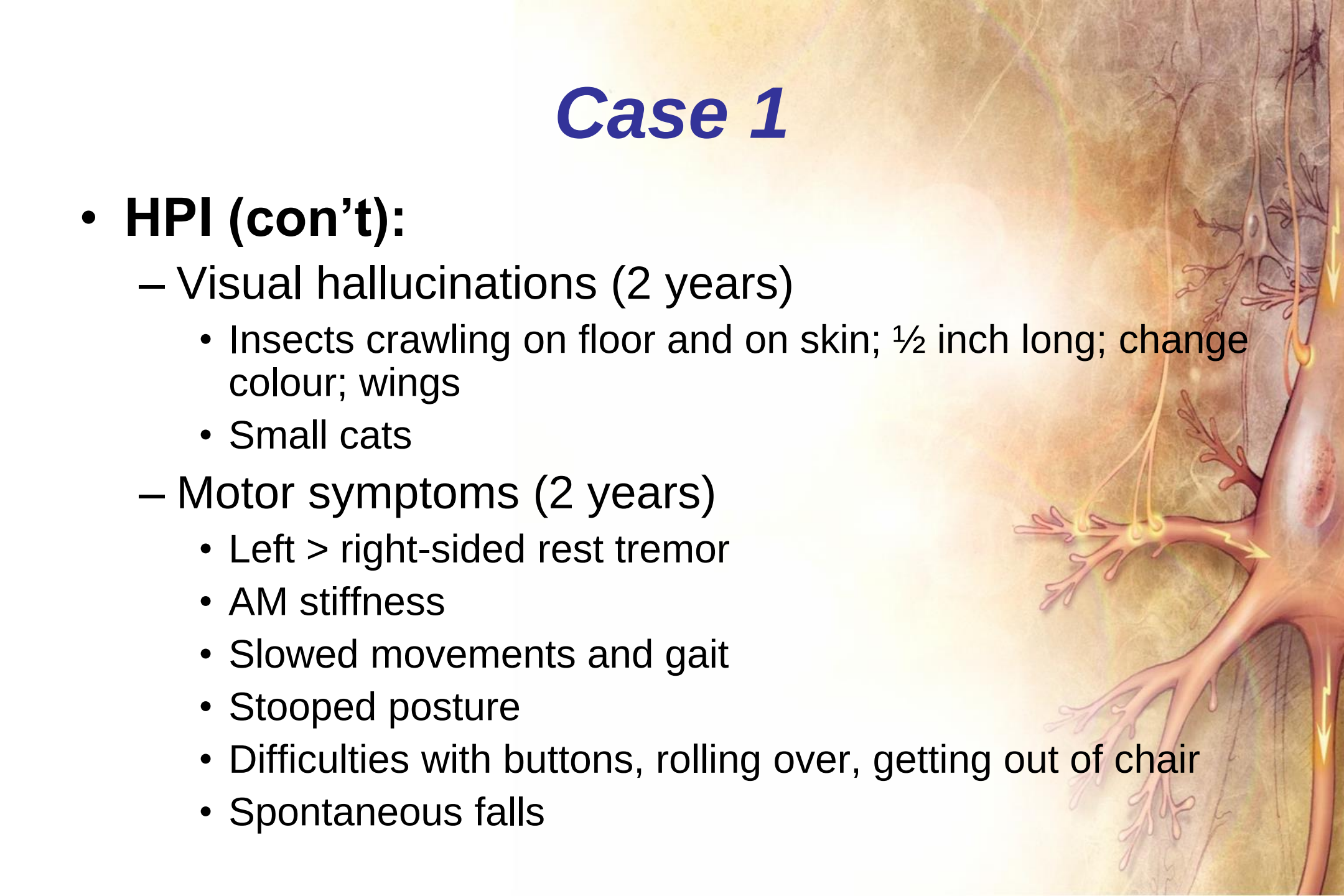
Case 1

- **HPI:**
  - Acting out dreams; flail arms and legs; being chased (3 years)
  - Insidious onset and gradual decline in cognition (2 years)
    - Losing train of thought
    - Word-finding troubles
    - Difficulties understanding complex instructions/written text
    - Mild ST memory loss – benefits from cueing
    - Cognitive fluctuations – occasional confusional episodes



Case 1

- **HPI (con't):**
  - Visual hallucinations (2 years)
    - Insects crawling on floor and on skin; ½ inch long; change colour; wings
    - Small cats
  - Motor symptoms (2 years)
    - Left > right-sided rest tremor
    - AM stiffness
    - Slowed movements and gait
    - Stooped posture
    - Difficulties with buttons, rolling over, getting out of chair
    - Spontaneous falls



Case 1

- **Exam:**
  - Vitals normal; no postural change
  - General exam normal
  - Cognitive exam
    - MMSE = 22/30
    - MOCA = 21/30
    - Behavioural Neurology Assessment-sf = 71/114
      - Inattention
      - Visuospatial dysfunction
      - Executive functions impaired
      - Naming
      - Verbal memory – benefited from cueing

Case 1

- **Exam:**
  - Neurological exam
    - Full EOM with no vertical gaze restrictions
    - Horizontal saccadic pursuit
    - Mild hypomimia & reduced blink
    - Hypophonia
    - L > R rest tremor; intermittent tremor R foot
    - L > R rigidity
    - L > R bradykinesia
    - Multiple attempts to arise from chair; posture stooped
    - Gait slow, festinating, reduced arm swing
    - Pull test – fall if not caught

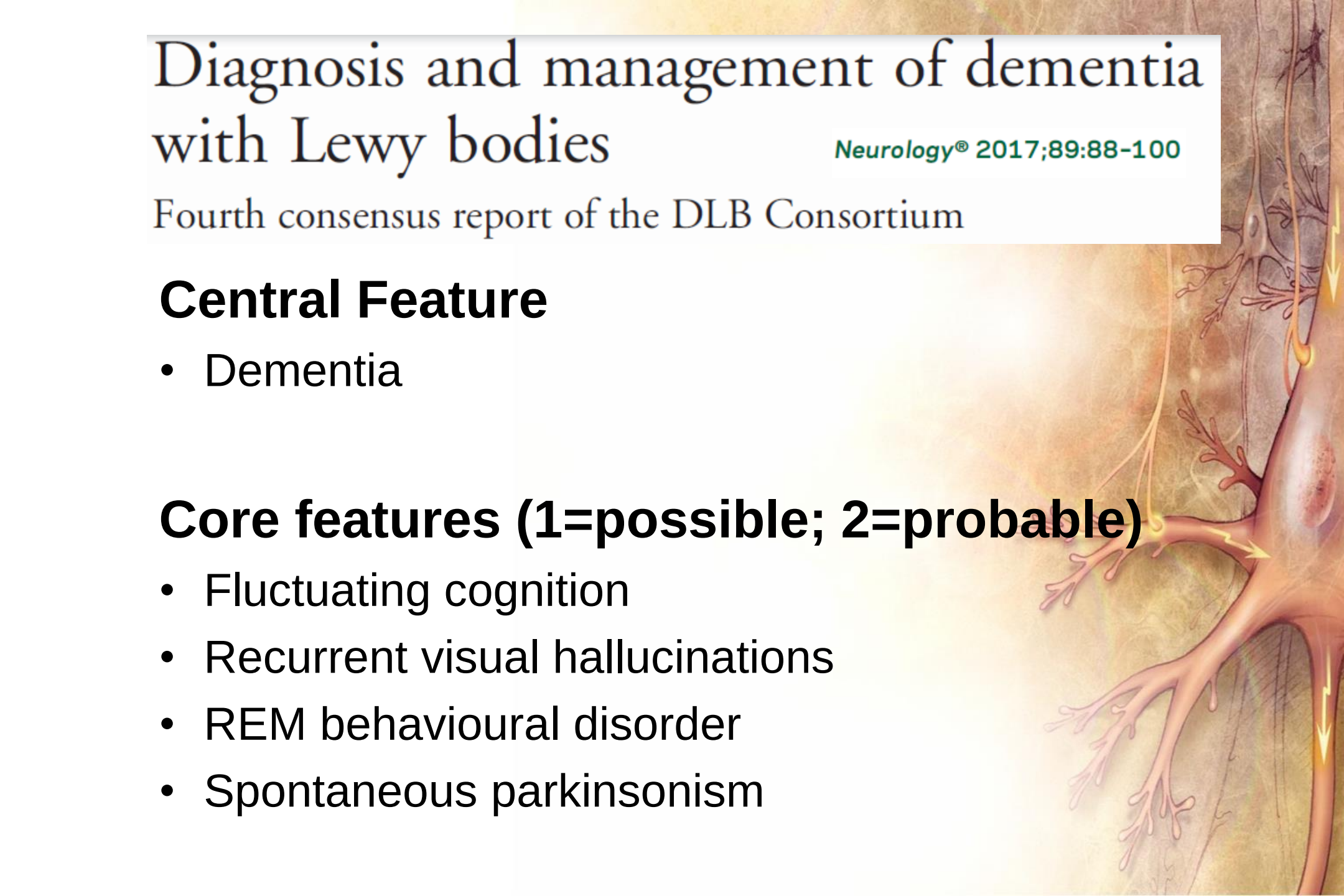
Diagnosis?

Dementia with Lewy Bodies

Diagnosis and management of dementia with Lewy bodies

Neurology® 2017;89:88-100

Fourth consensus report of the DLB Consortium



Central Feature

- Dementia

Core features (1=possible; 2=probable)

- Fluctuating cognition
- Recurrent visual hallucinations
- REM behavioural disorder
- Spontaneous parkinsonism

Diagnosis and management of dementia with Lewy bodies

Neurology® 2017;89:88-100

Fourth consensus report of the DLB Consortium

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

Diagnosis and management of dementia with Lewy bodies

Neurology® 2017;89:88-100

Fourth consensus report of the DLB Consortium

Probable DLB can be diagnosed if:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or

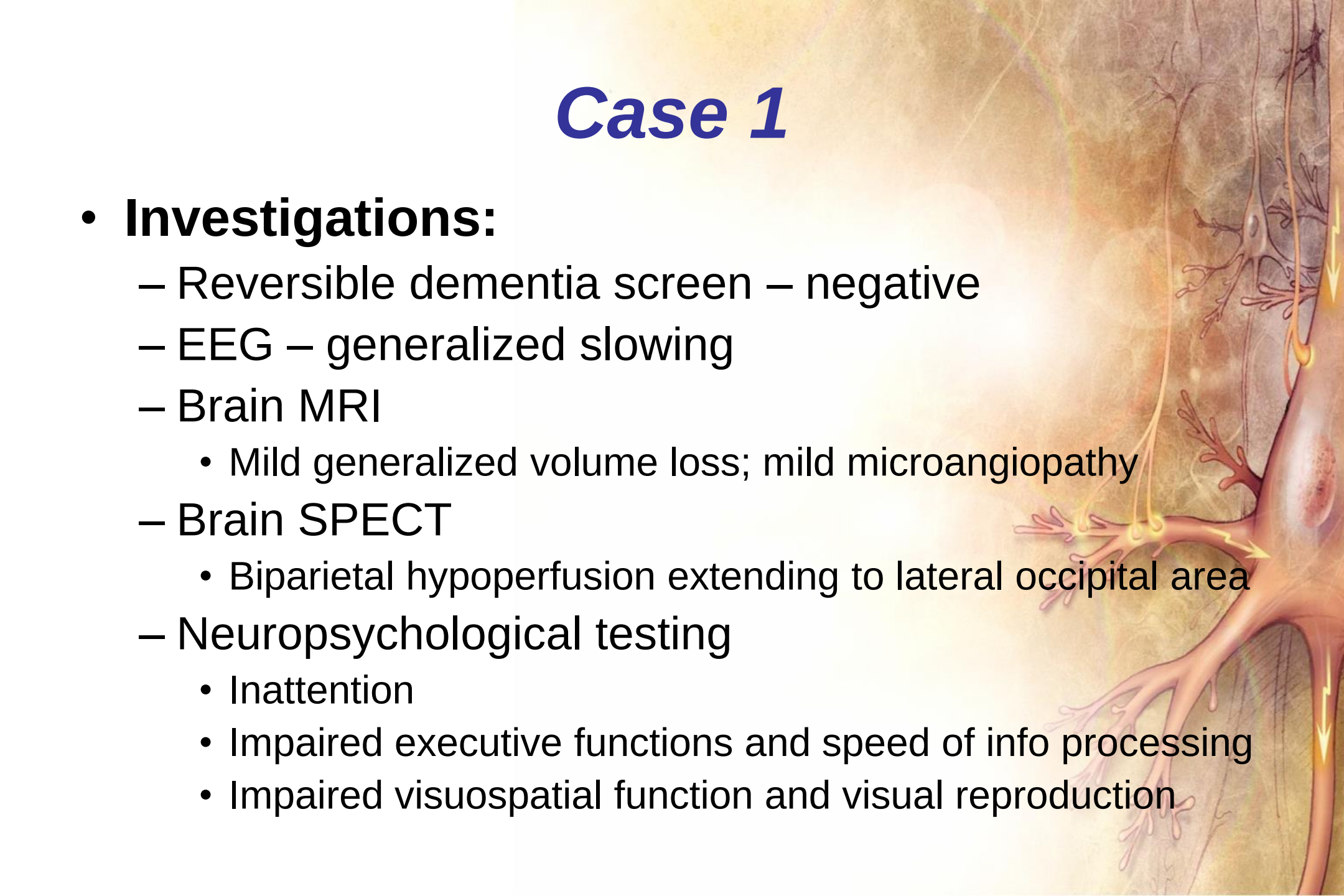
b. One or more indicative biomarkers is present but there are no core clinical features.

Epidemiology of DLB

- Second most common form of degenerative dementia
- 10-15% of dementia cases at autopsy (McKeith et al., 1996)
- Community-based study 5% met consensus criteria of DLB (age > 85 years); represents ~ 22% of all demented cases (Rahkonen et al., 2003)

Case 1

- **Investigations:**
  - Reversible dementia screen – negative
  - EEG – generalized slowing
  - Brain MRI
    - Mild generalized volume loss; mild microangiopathy
  - Brain SPECT
    - Biparietal hypoperfusion extending to lateral occipital area
  - Neuropsychological testing
    - Inattention
    - Impaired executive functions and speed of info processing
    - Impaired visuospatial function and visual reproduction

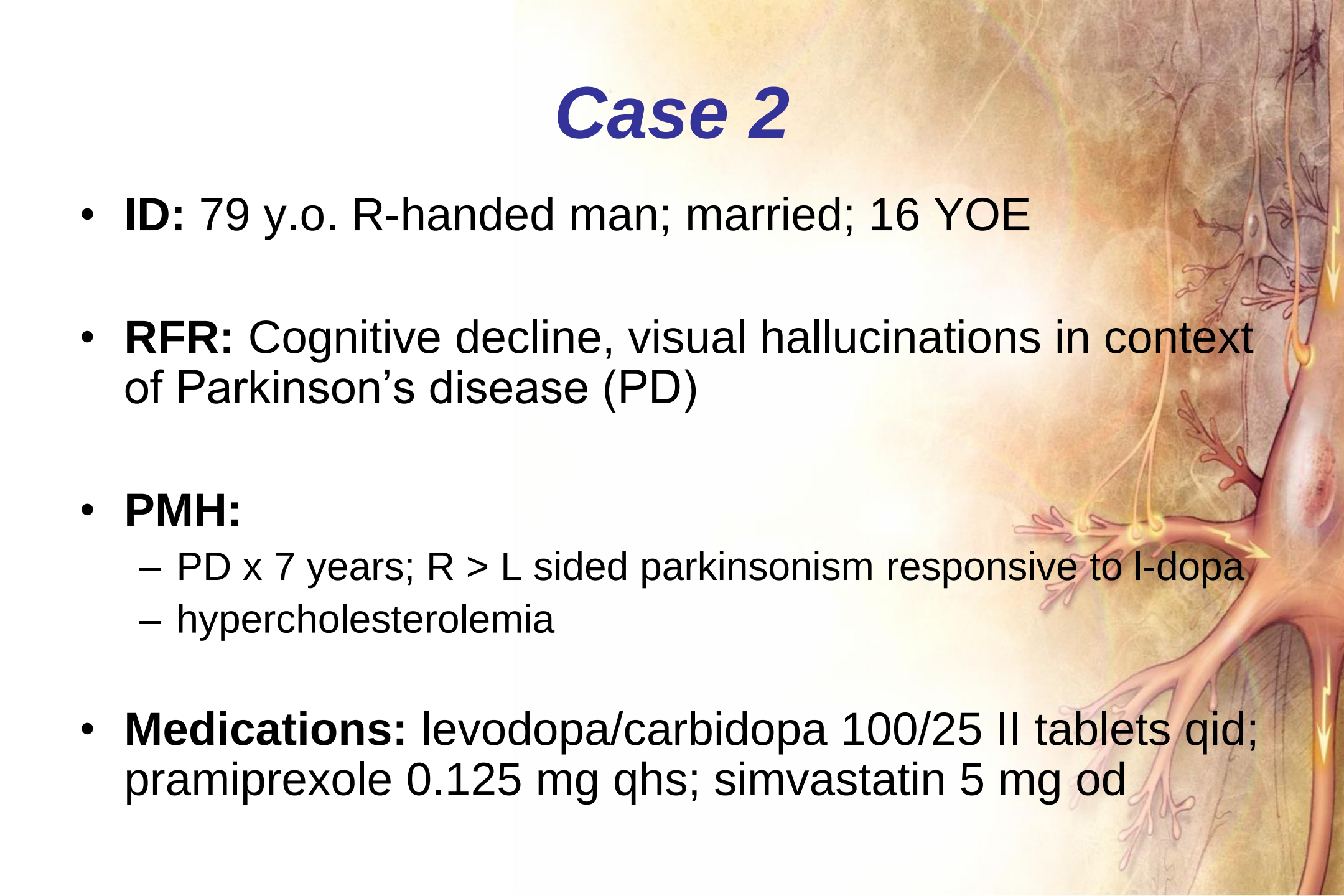


Treatment?

Case 2

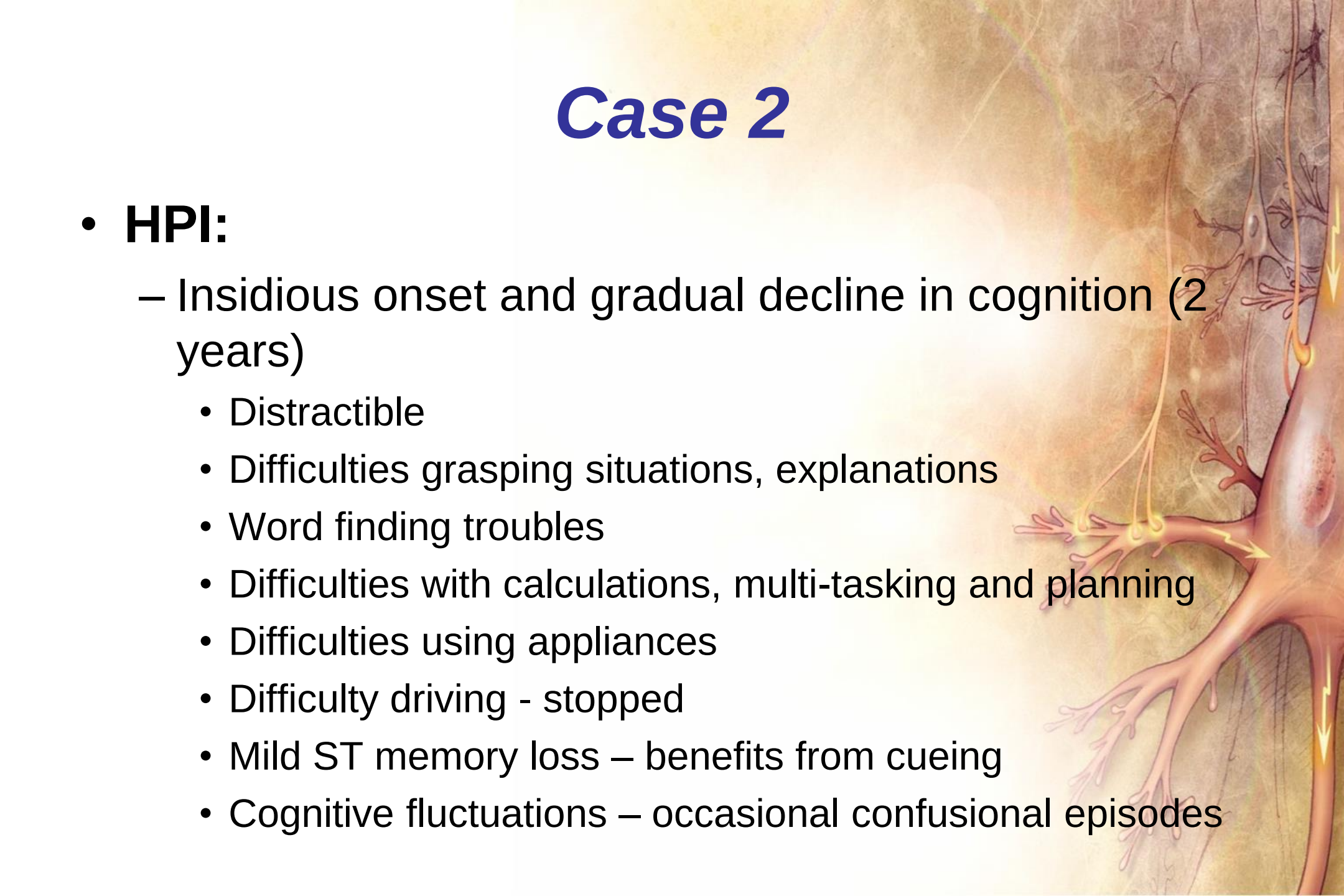
Case 2

- **ID:** 79 y.o. R-handed man; married; 16 YOE
- **RFR:** Cognitive decline, visual hallucinations in context of Parkinson's disease (PD)
- **PMH:**
  - PD x 7 years; R > L sided parkinsonism responsive to l-dopa
  - hypercholesterolemia
- **Medications:** levodopa/carbidopa 100/25 II tablets qid; pramiprexole 0.125 mg qhs; simvastatin 5 mg od



Case 2

- **HPI:**
  - Insidious onset and gradual decline in cognition (2 years)
    - Distractible
    - Difficulties grasping situations, explanations
    - Word finding troubles
    - Difficulties with calculations, multi-tasking and planning
    - Difficulties using appliances
    - Difficulty driving - stopped
    - Mild ST memory loss – benefits from cueing
    - Cognitive fluctuations – occasional confusional episodes

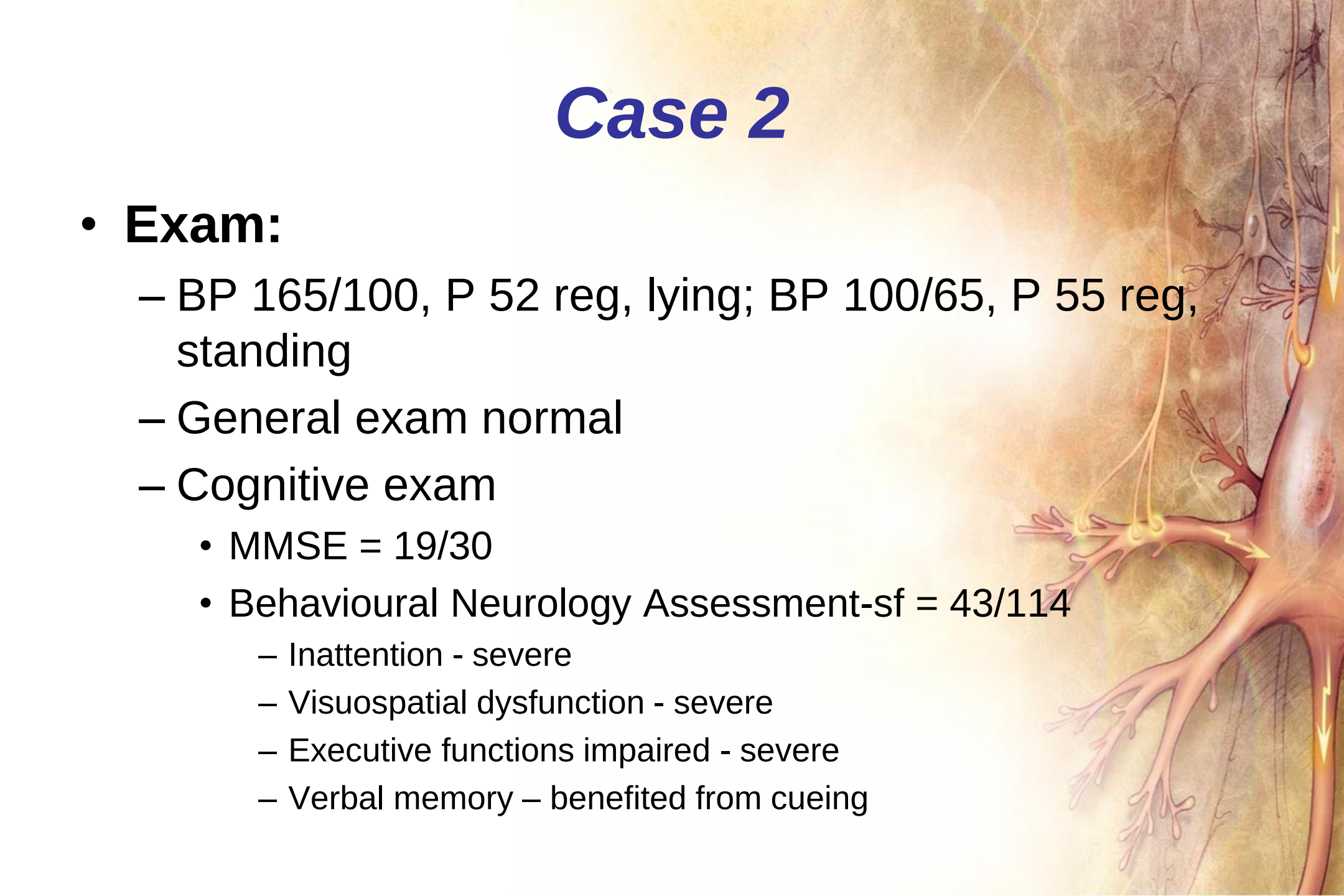


Case 2

- **HPI (con't):**
  - Neuropsychiatric symptoms (2 years)
    - Occasional visual hallucinations
      - "bird swooping across the room"
    - Occasional concerns that wife was having affair
  - Autonomic symptoms
    - Postural dizziness
    - One prior pre-syncopal episode
    - No history of unexplained syncope, arrhythmia, cardiac disease

Case 2

- **Exam:**
  - BP 165/100, P 52 reg, lying; BP 100/65, P 55 reg, standing
  - General exam normal
  - Cognitive exam
    - MMSE = 19/30
    - Behavioural Neurology Assessment-sf = 43/114
      - Inattention - severe
      - Visuospatial dysfunction - severe
      - Executive functions impaired - severe
      - Verbal memory – benefited from cueing

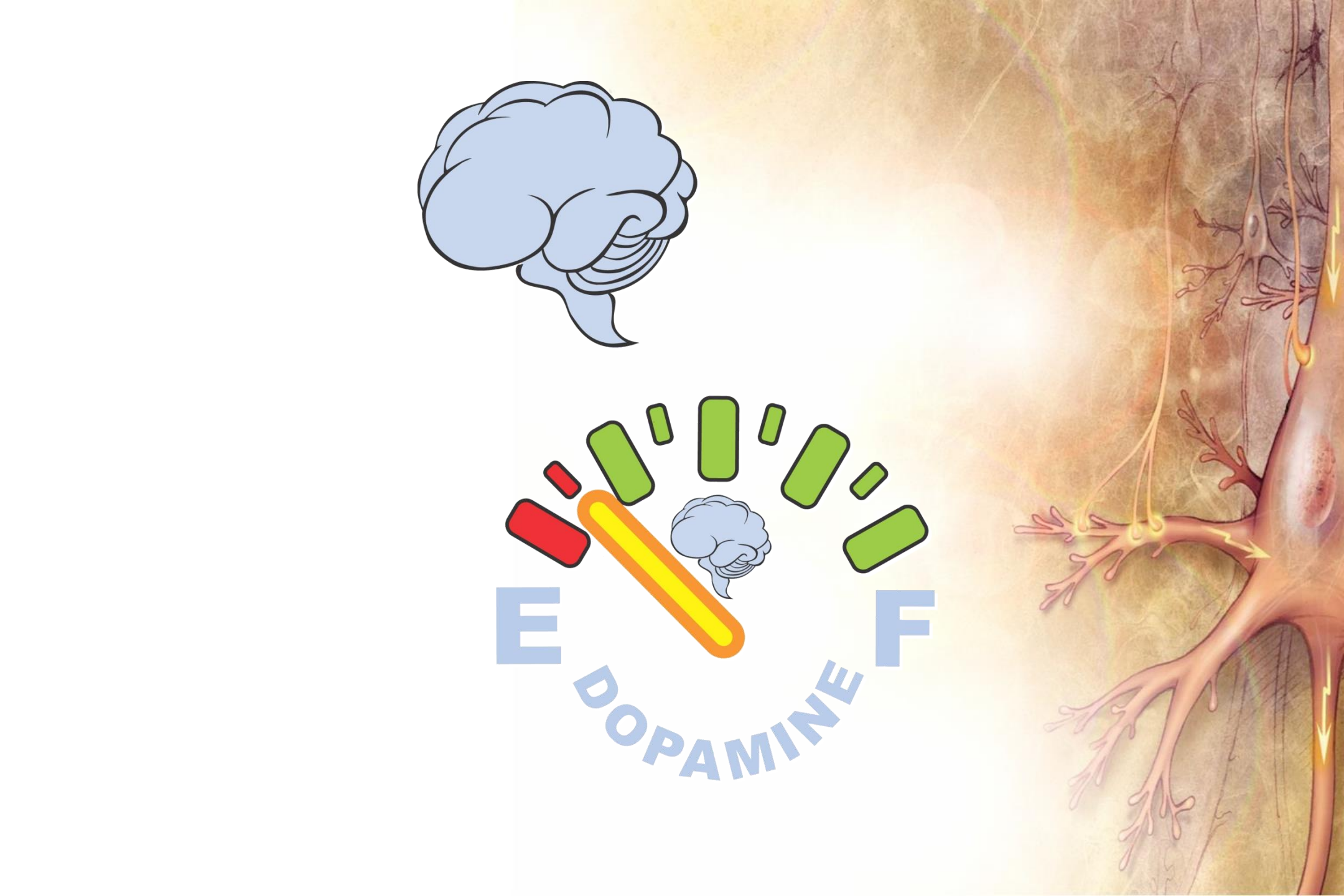


Case 2

- **Exam:**
  - Neurological exam
    - Full EOM with no vertical gaze restrictions
    - Horizontal saccadic pursuit
    - Moderate hypomimia & reduced blink
    - Hypophonia & mild dysarthria
    - R > L rest tremor
    - R > L rigidity
    - L > R bradykinesia
    - Multiple attempts to arise from chair; posture stooped
    - Gait reasonable normal with good arm swing
    - Pull test – fall if not caught

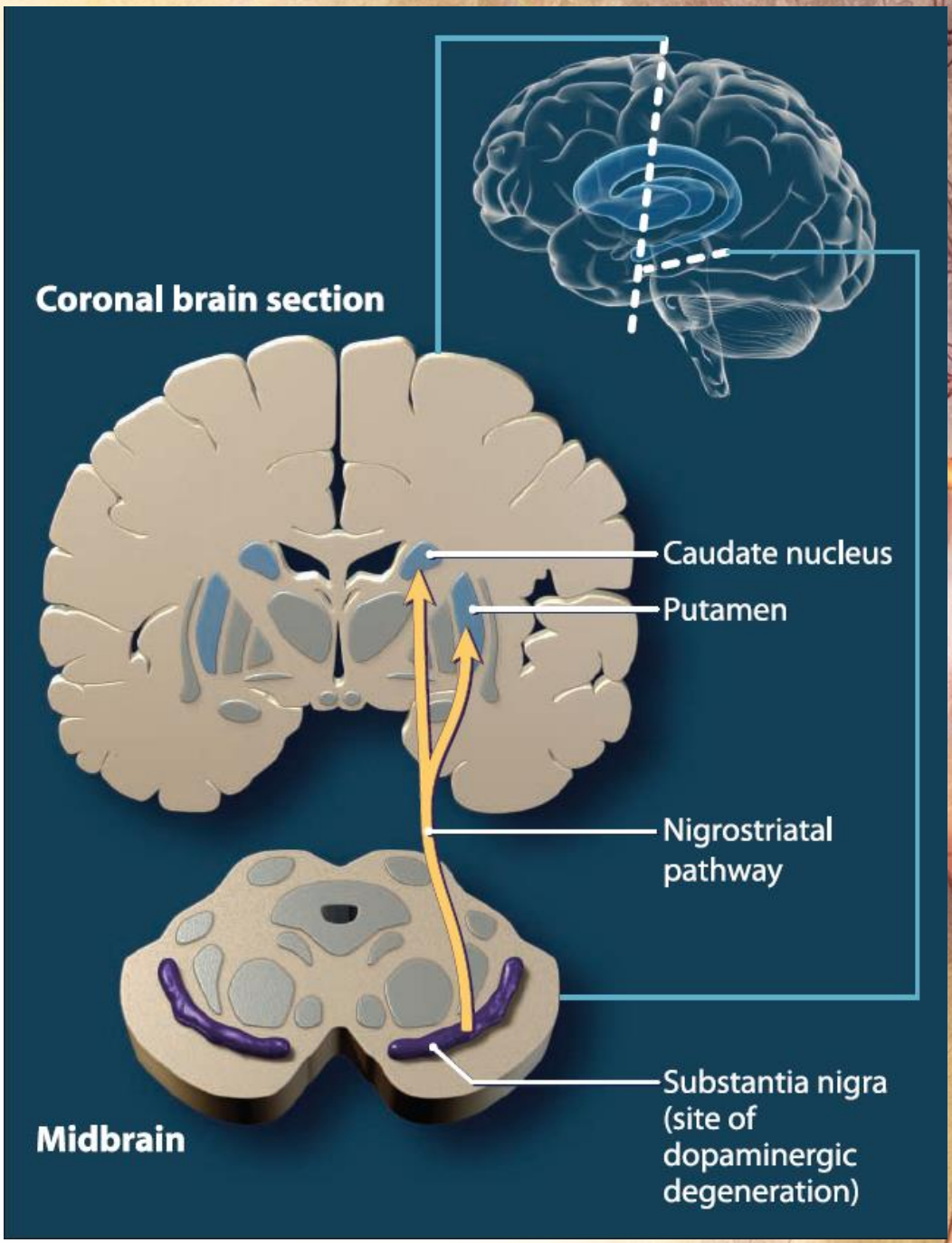
Diagnosis?

Parkinson’s disease dementia


E
DOPAMINE
F

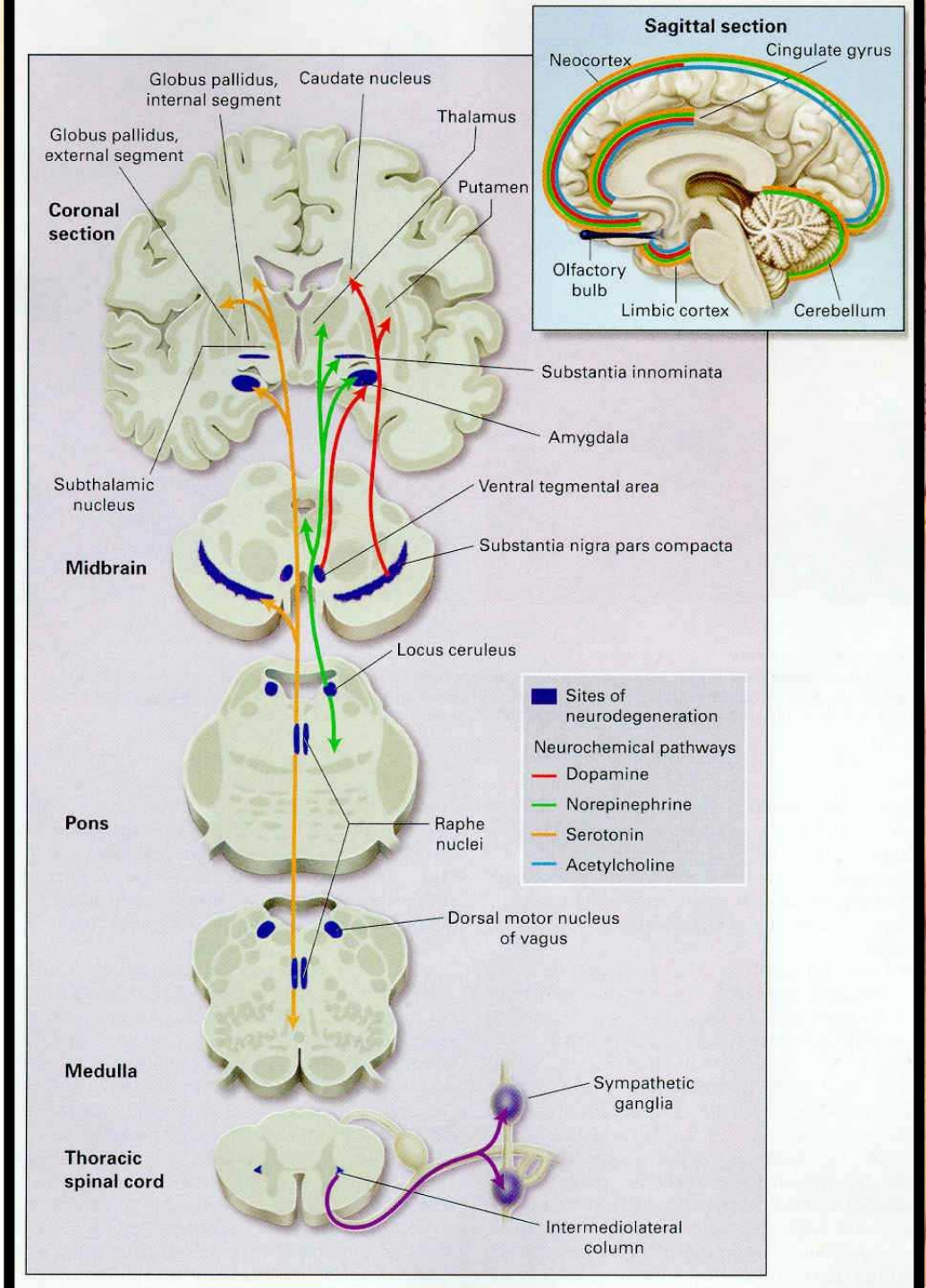
Pathophysiology of motor symptoms

(Guttman et al., 2003)



More than just dopamine….

(Lang & Lozano, 1998)



Diagnosing Parkinson's Disease Dementia

Diagnostic process:

- Diagnosis of PD – "TRAP"; asymmetry; levodopa response
- Diagnosis of dementia (after >1 year of motor symptoms)

> "Cognitive deficits severe and extensive enough to fulfill the DSM-IV criteria for the diagnosis of dementia"

DSM-IV criteria for dementia:

- Multiple cognitive deficits
  - Memory impairment
  - Aphasia, apraxia, agnosia or executive dysfunction
- Significant decline from previous level of functioning

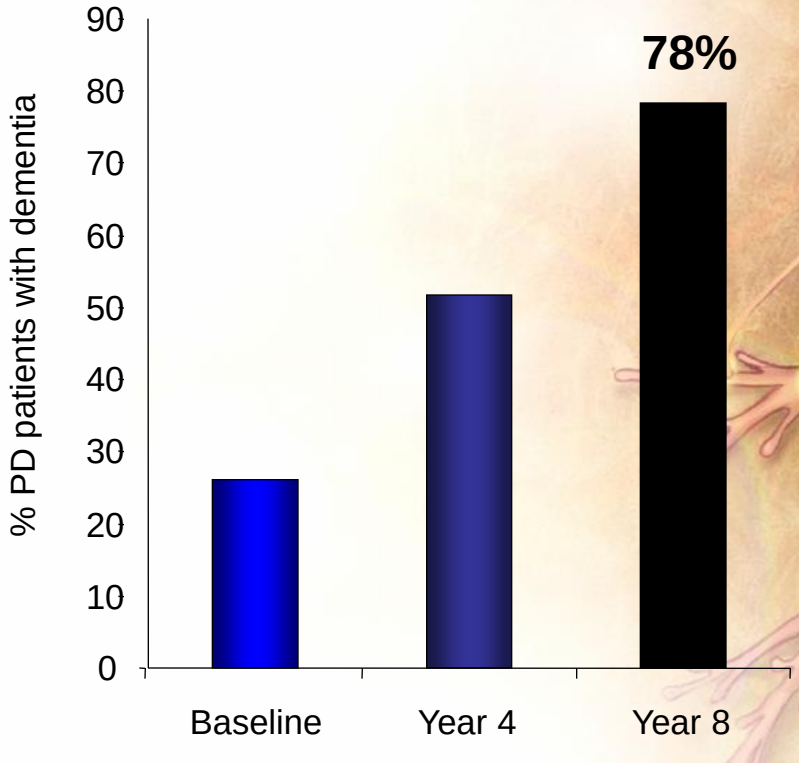
Emre M. *Lancet Neurol* 2003;2:229–37
DSM-IV 2000

Epidemiology of PDD

Prevalence:

- PD without dementia ~1.8% > 65 y.o. (de Rijk et al., 2000)
- ~ 100,000 Canadians
- ~ 40-50% of all PD patients develop dementia

- Incidence of dementia:
  - Occurs up to 6 times more often than in normal population



Aarsland et al., 2003; Cummings, 1988; Lang & Obeso, 2004

Risk Factors for developing Parkinson's Disease Dementia

- Age
- Atypical features of PD*
- Duration of disease
- Akinetic-rigid syndrome
- Motor disability
- Confusion or psychosis with Levodopa therapy
- Depression

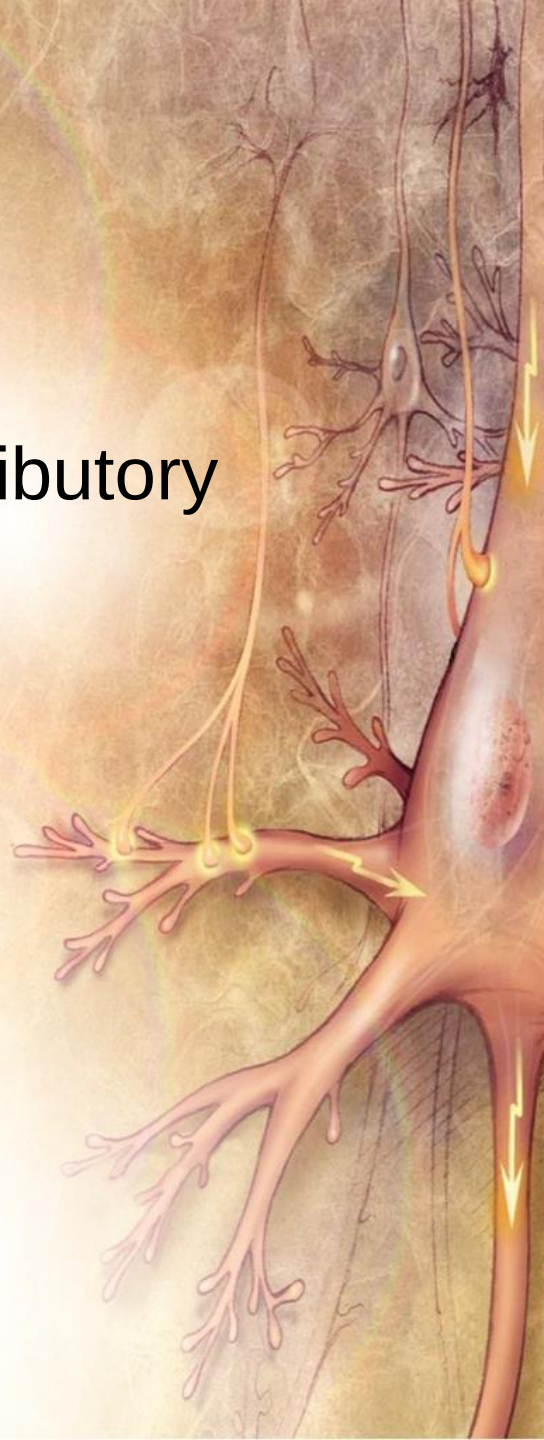
Mayeux R *et al*. *Arch Neurol* 1992;49:492–7
Emre M. *Lancet Neurol* 2003;2:229–37

Atypical Features

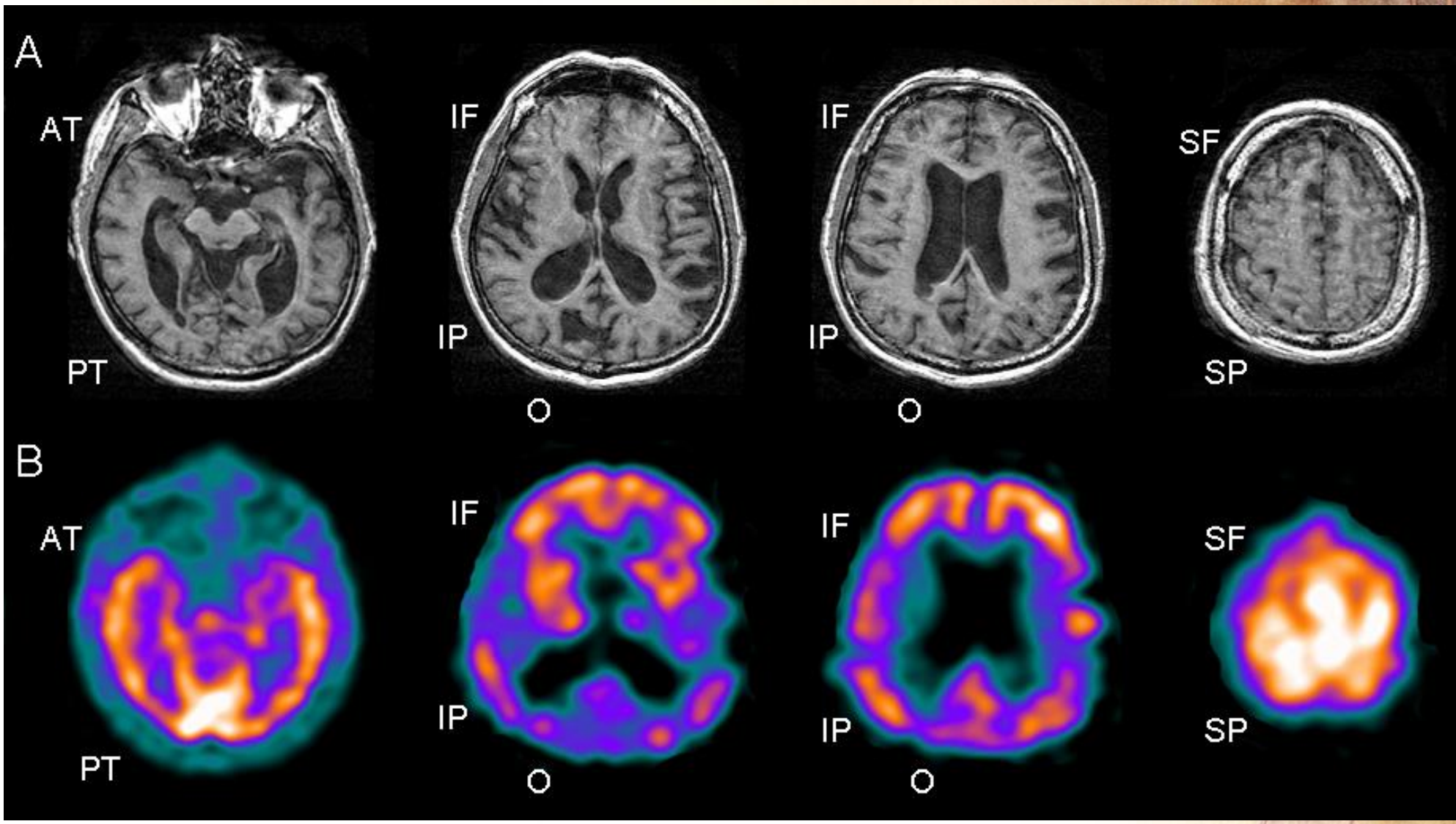
- Early falls
- Poor response to levodopa
- Symmetry at onset
- Rapid progression
- Lack of tremor
- Dysautonomia
  - Urinary urgency/incontinence
  - Urinary retention
  - Fecal incontinence
  - Persistent erectile dysfunction
  - Orthostatic hypotension

Case 2

- **Investigations:**
  - Reversible dementia screen – non-contributory
  - Neuropsychological testing
    - Global impairments
      - Attention and working memory deficits
      - Impaired executive functions - severe
      - Impaired visuospatial function – severe
      - Impaired verbal episodic memory
      - Impaired semantic and phonemic fluency



Neuroimaging



Diagnosis?

Parkinson’s disease dementia

±

Alzheimer’s disease

Treatment?

Comparing DLB and PDD

Clinical Differentiation of PDD and DLB

PDD:

- **Common symptoms**
  - **Motor symptoms**
  - **Visual hallucinations**
  - **Cognitive decline**
  - **Cognitive fluctuations**
- **Dementia occurs *after* motor symptoms**
- **Lewy body pathology**

DLB:

- **Common symptoms**
  - **Motor symptoms**
  - **Visual hallucinations**
  - **Cognitive decline**
  - **Cognitive fluctuations**
- **Dementia occurs *before* motor symptoms**
- **Lewy body pathology**

~ 20% of all dementia cases

Emre M. *Lancet Neurol* 2003;2:229–37
McKeith I *et al*. *Lancet Neurol* 2004;3:19–28

Comparing PDD, DLB and AD

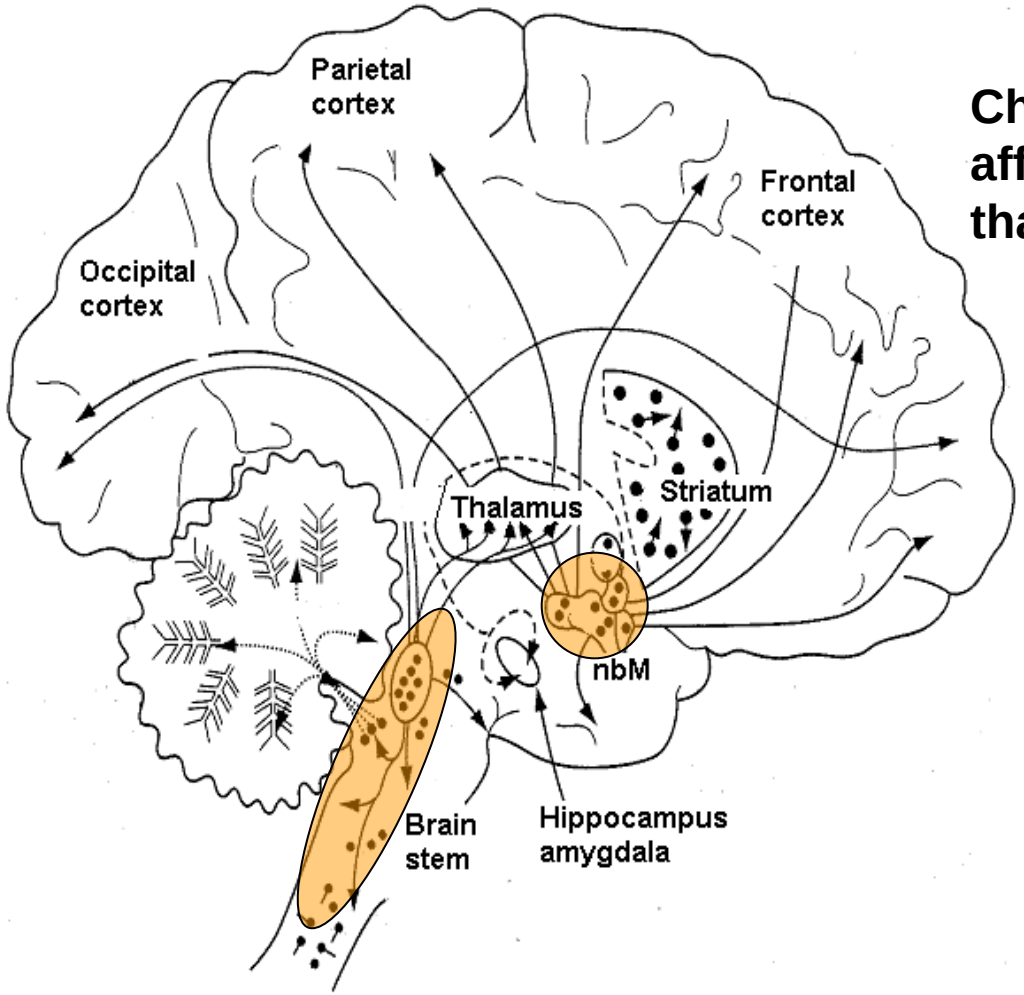
	PDD	DLB	AD
Pathological hallmark	Lewy bodies	Lewy bodies + Plaques/tangles	Plaques/tangles
Cholinergic deficits	+++	+++	++
Dopaminergic deficits	+++	++	+/-
Predominant brain region affected	Cortical/ fronto-subcortical circuits	Cortical/ fronto-subcortical circuits	Cortical/ Hippocampus
Main cognitive impairments	Dysexecutive/ Attention/VS	Dysexecutive/ Attention/VS	Memory
Motor symptoms	Yes - typical	Usually - atypical	Rarely

Ince PG et al. Brain Pathology 1998;8:299–324.

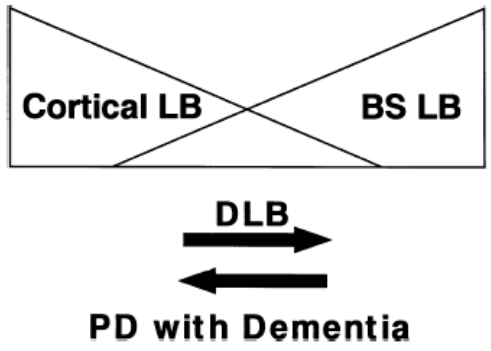
Ala TA et al. Int J Geriatr Psychiatry 2002;17:503–9

Burn DJ, et al. *Mov Disord* 2003;18 (Suppl 6):S72–9.

Neurochemistry of DLB and PDD: Cognition and neuropsychiatry

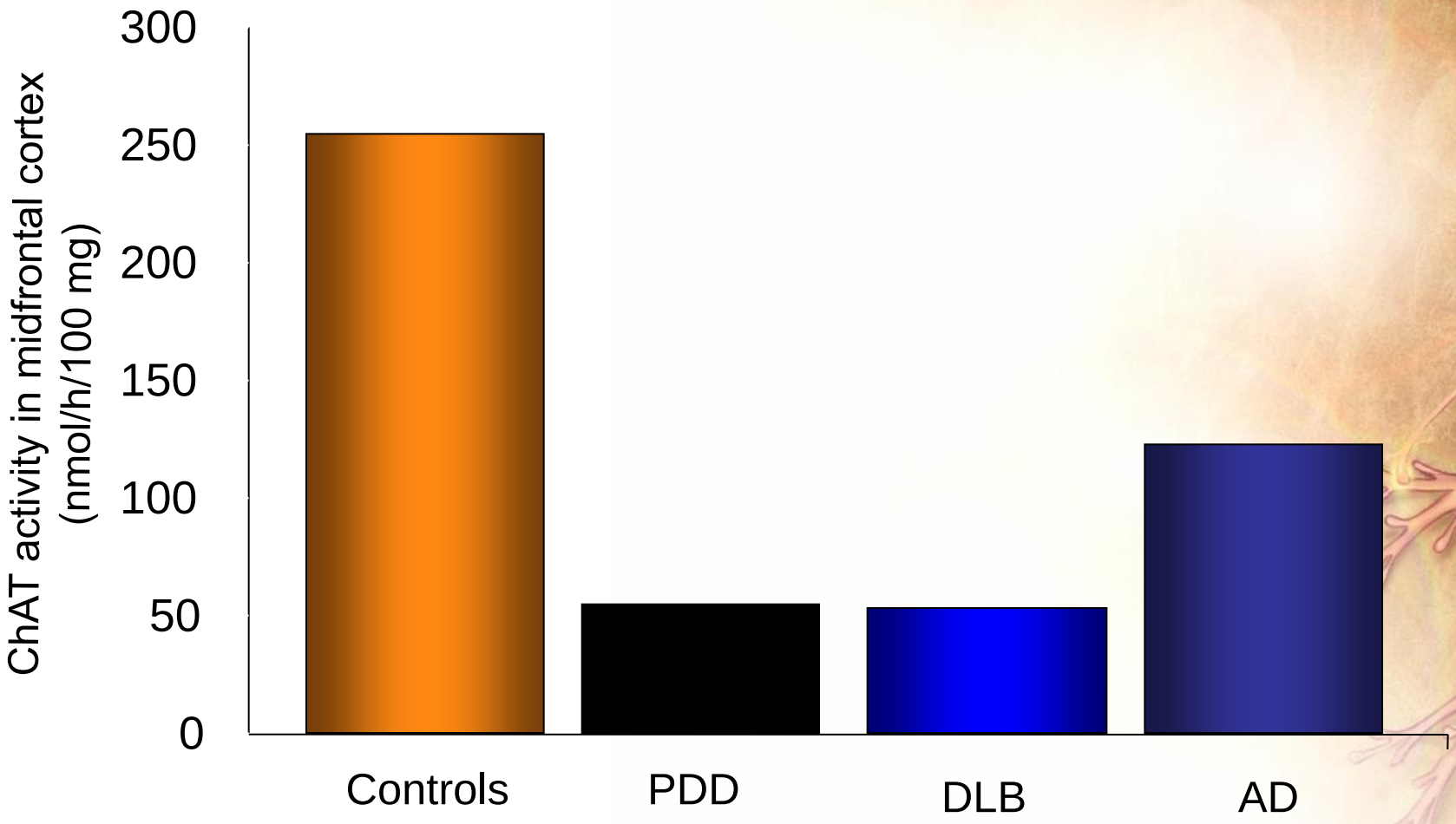


Cholinergic loss in PDD and DLB affects frontostriatal-thalamocortical circuits



Perry et al., 1999; Mori, 2002

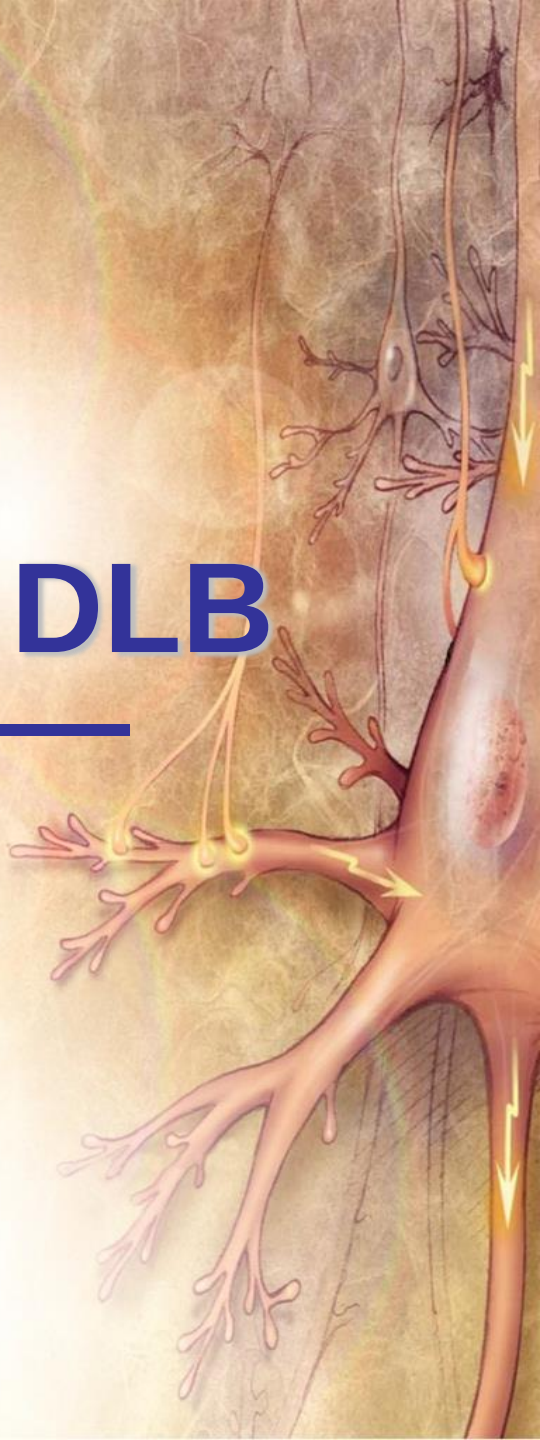
Common Cholinergic Deficits in PDD and DLB



Tiraboschi et al., 2000

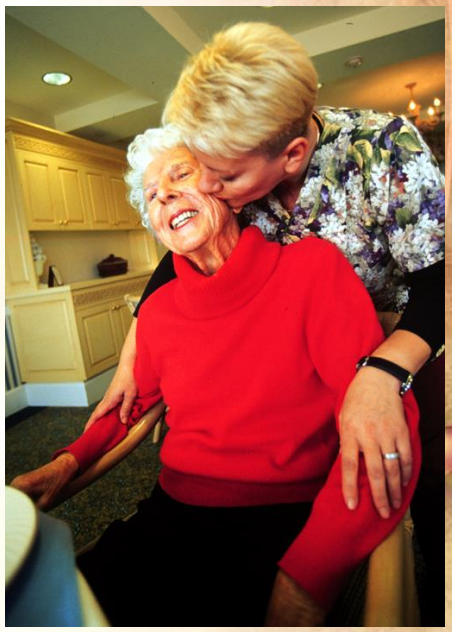
Treatment of PDD and DLB

The Rationale and the Challenges



Impact of PDD and DLB: Reduced Patient Quality of Life

- Difficulty with everyday tasks such as eating, dressing or shopping
- Become apathetic, depressed and withdrawn from family life
- Less able to plan, organize and perform goals
- Difficulty with memory and verbal fluency



Actual patient not shown

Emre M. *Lancet Neurol* 2003;2:229–37

Drug Treatment in PDD and DLB

Treatment targets:

- Motor symptoms
- Cognitive deficits related to dementia
- Mood and Behavioural symptoms
  - Apathy
  - Anxiety
  - Depression
  - Hallucinations
- Daily functioning

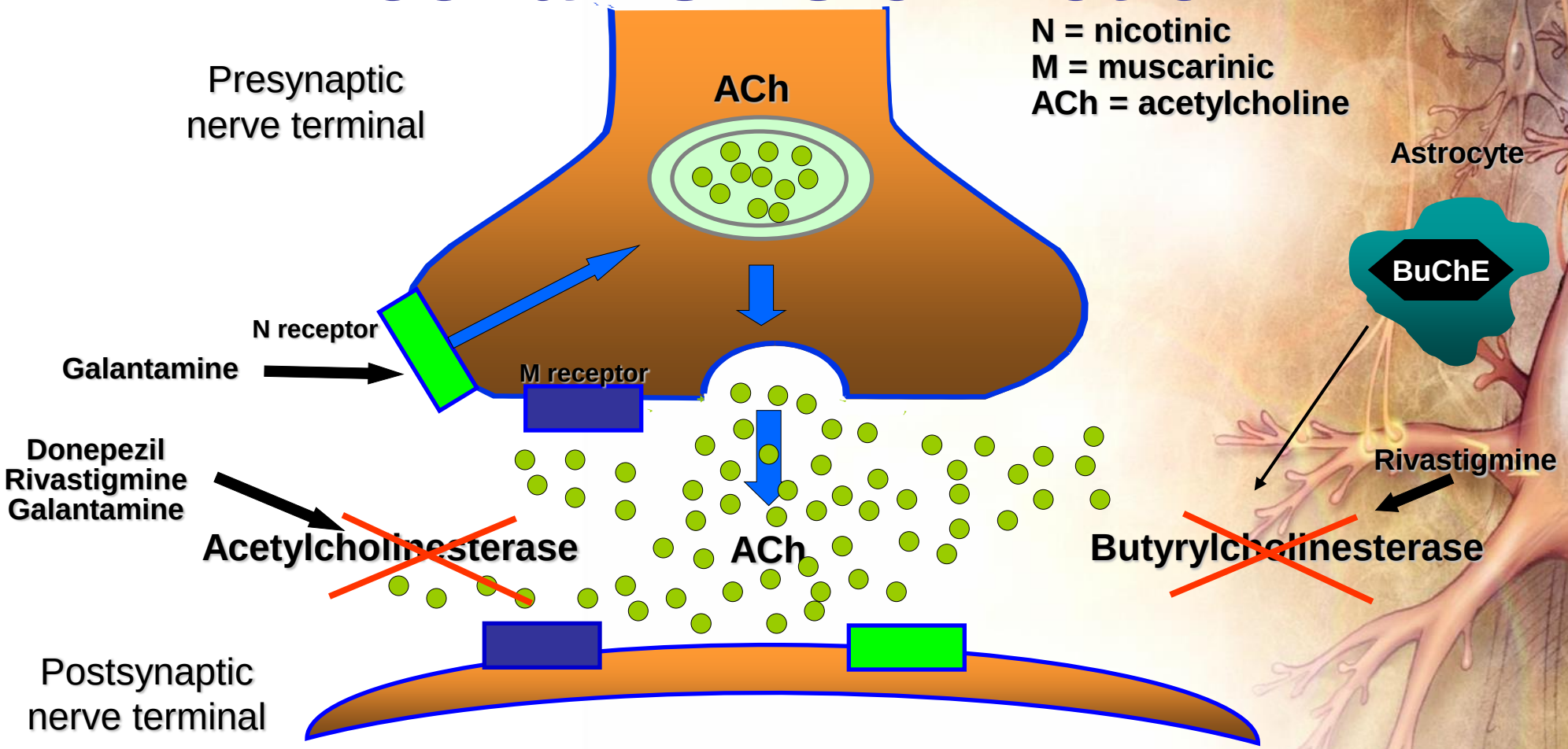
The Challenge of Treating the Symptoms of PDD and DLB

Agents used to treat EPS	Conventional Antipsychotics	Atypical Antipsychotics
↓	↓	↓
No improvements in cognitive function	EPS, sedation, confusion, falls, sensitivity reactions	Anticholinergic effects, sedation

Need for alternative therapies to treat the cognitive, mood and behavioural symptoms

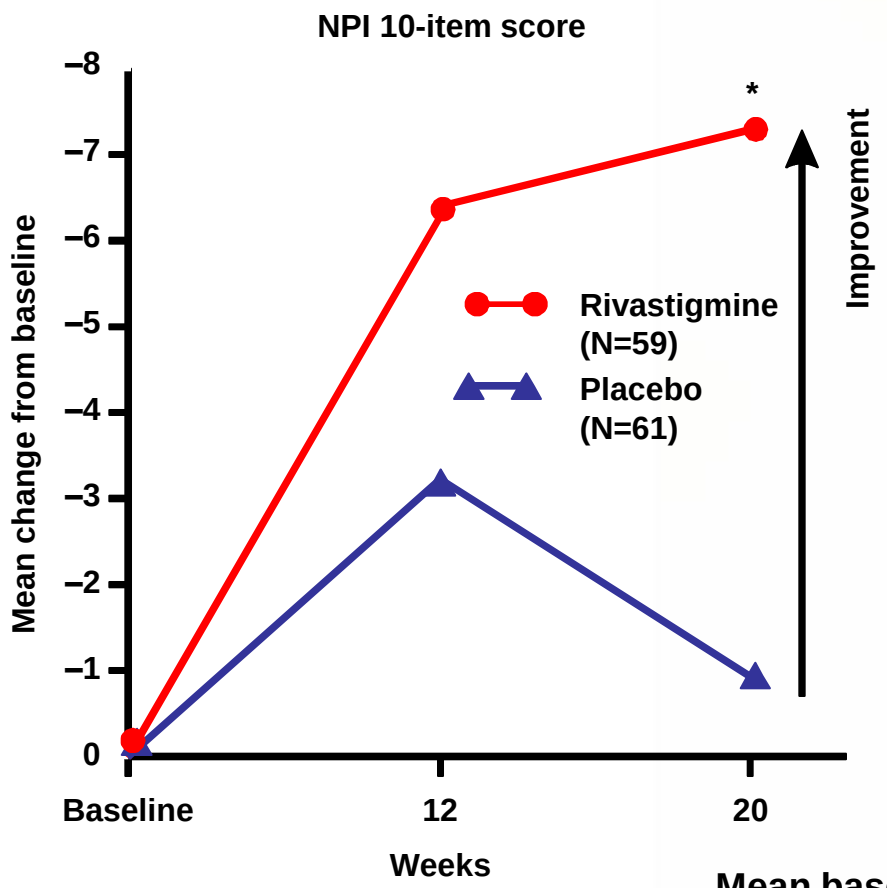
Emre M. *Lancet Neurol* 2003;2:229–37
McKeith I *et al*. *Lancet Neurol* 2004;3:19–28
Burn DJ, McKeith IG. *Mov Disord* 2003;18 (Suppl 6):S72–9

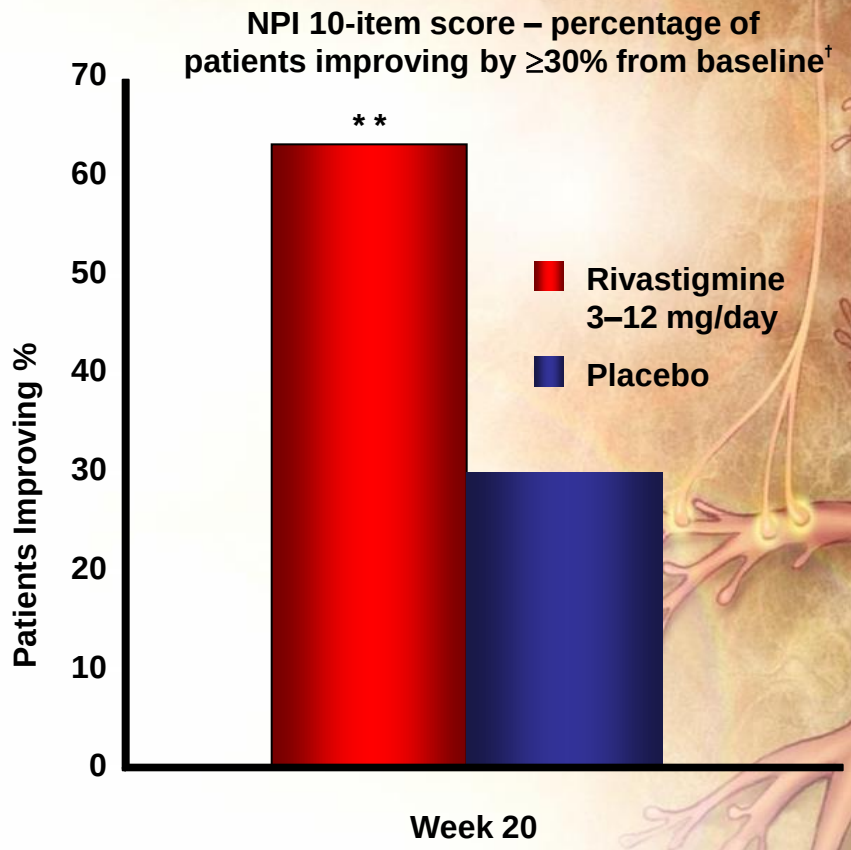
Cholinesterase Inhibitors: Mechanisms of Action



Increased availability of ACh at synapse (AChE and BuChE inhibition)

Efficacy of rivastigmine on neuropsychiatric symptoms in DLB





Mean baseline scores	Riva.	Plac.
NPI-10	23.2	20.2
MMSE	17.9	17.8

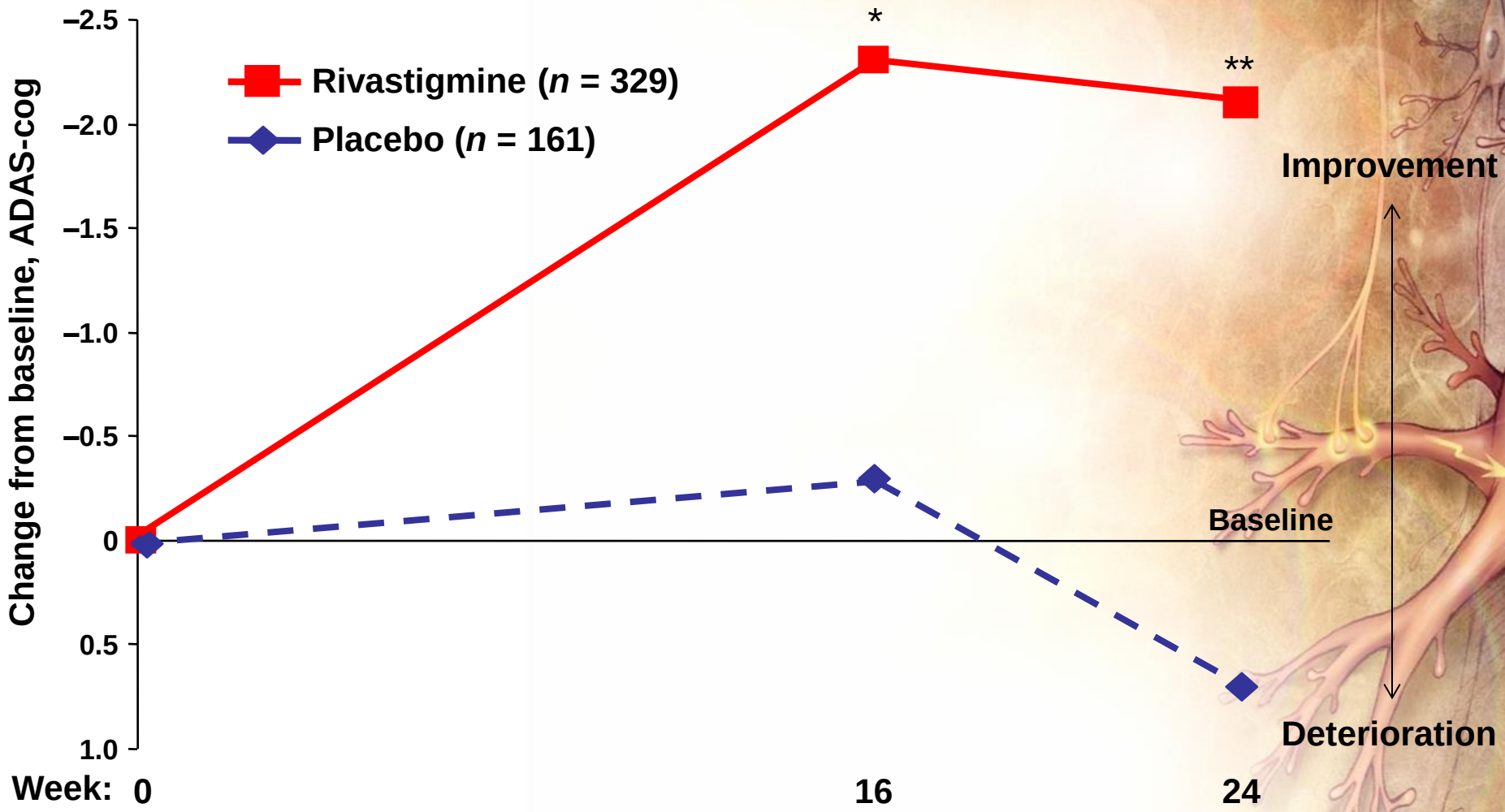
OC analysis

*p=0.005 vs placebo; **p=0.001 vs placebo

†Responder definition recommended by NPI author (J Cummings)

McKeith et al., 2000

Rivastigmine in PDD: Significant benefits on cognition

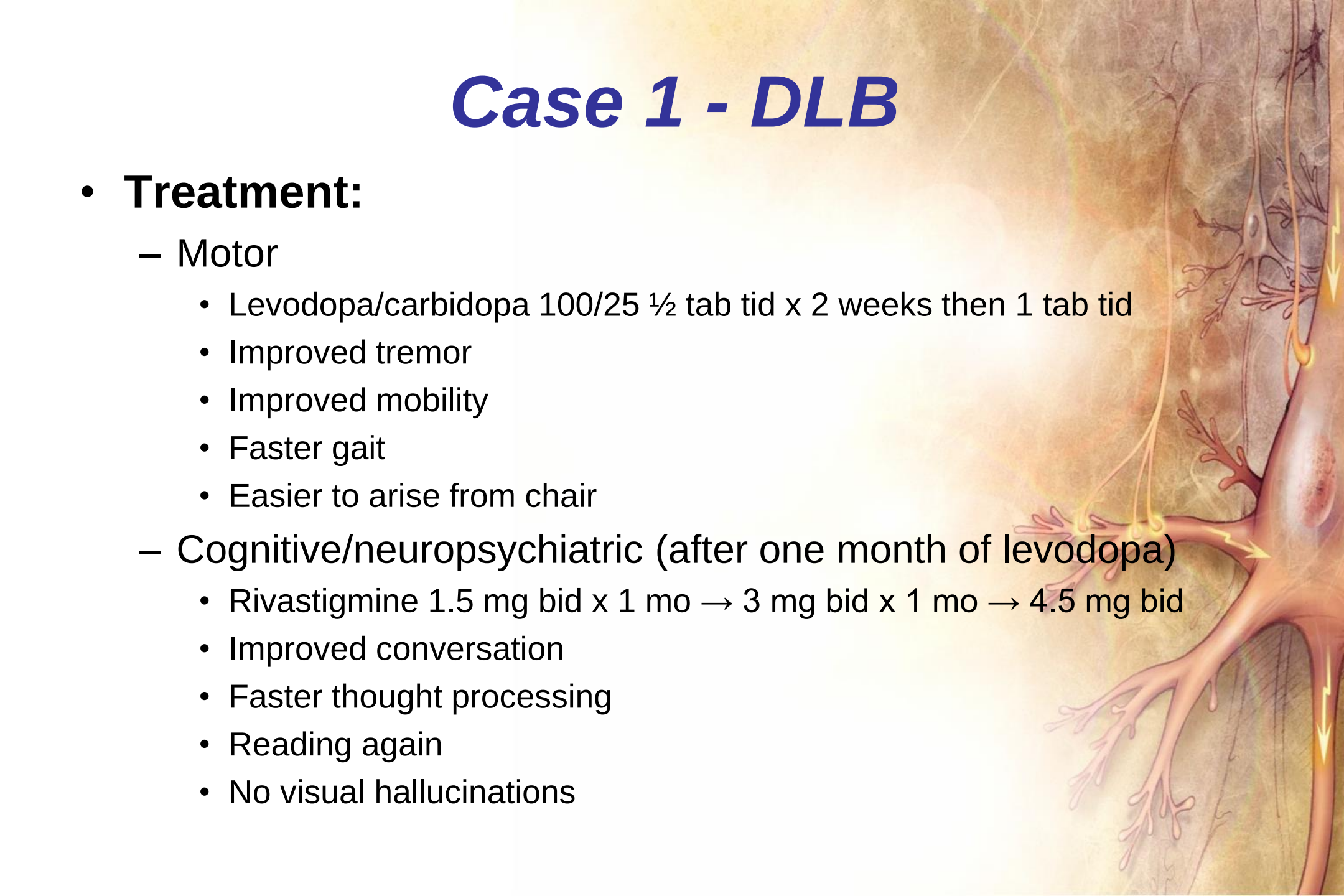


*p = 0.002; **p < 0.001, ITT-RDO analysis

Emre et al., 2004

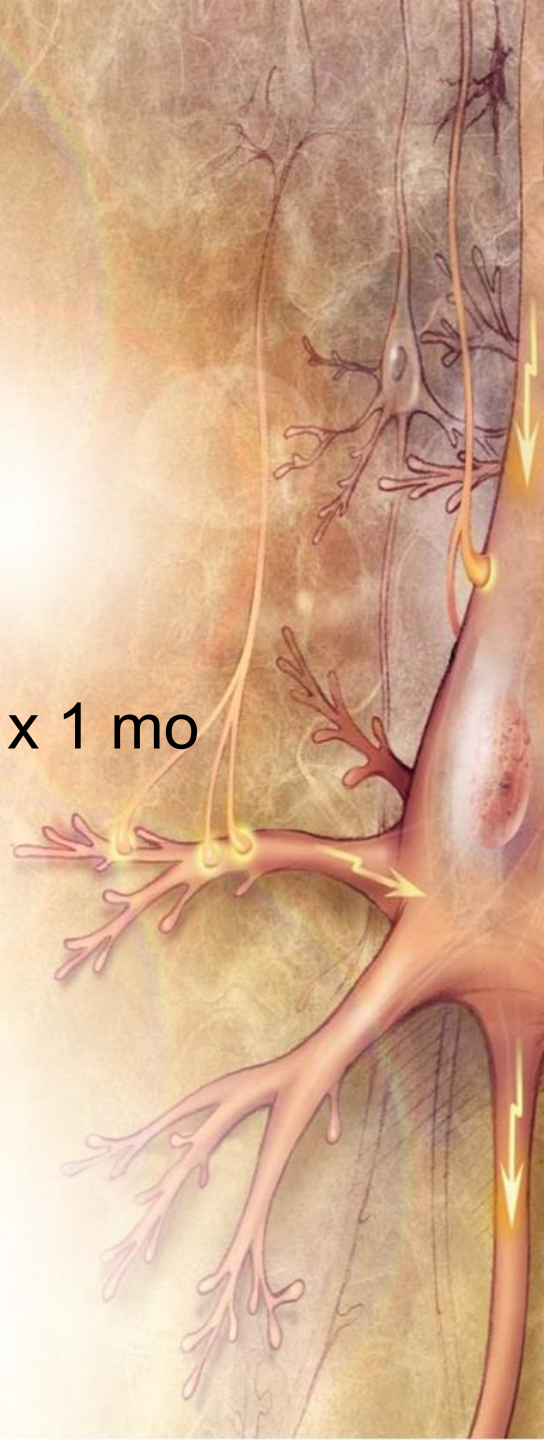
Case 1 - DLB

- **Treatment:**
  - Motor
    - Levodopa/carbidopa 100/25 ½ tab tid x 2 weeks then 1 tab tid
    - Improved tremor
    - Improved mobility
    - Faster gait
    - Easier to arise from chair
  - Cognitive/neuropsychiatric (after one month of levodopa)
    - Rivastigmine 1.5 mg bid x 1 mo → 3 mg bid x 1 mo → 4.5 mg bid
    - Improved conversation
    - Faster thought processing
    - Reading again
    - No visual hallucinations



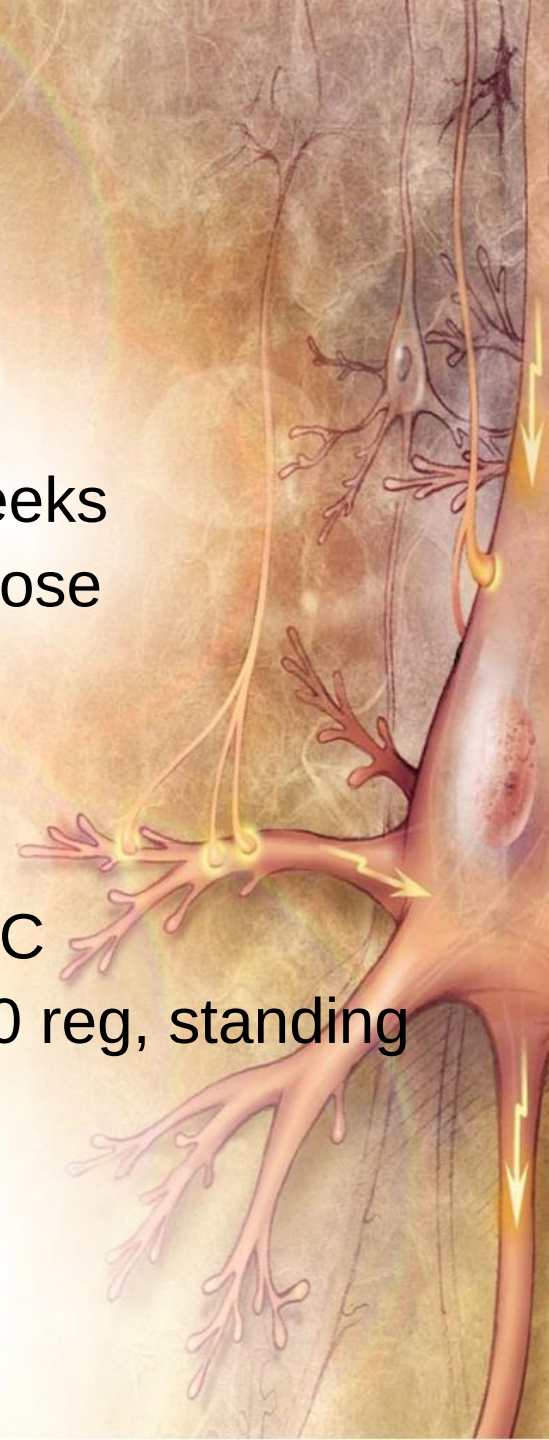
Case 2 - PDD

- **Treatment:**
  - Motor
    - No change in dopaminergic drugs
  - Cognitive/neuropsychiatric
    - Rivastigmine 1.5 mg bid x 1 mo → 3 mg bid x 1 mo
    - Improved conversation
    - More alert and engaged
    - Less fluctuations
    - Improved train of thought
    - Grasping situations better, e.g., finances
    - No visual hallucinations or delusions



Case 2

- **Treatment (con't):**
  - Cognitive/neuropsychiatric
    - Rivastigmine increased to 4.5 mg bid x 2 weeks
    - Cognitively, no additional benefit at higher dose
    - MMSE = 24/30
  - Autonomic
    - Worsening orthostasis and fatigue
    - Two presyncopal events – collapsed; no LOC
    - BP 110/60, P 50 reg, supine; BP 75/45, P 60 reg, standing
    - No gastrointestinal intolerance
    - No clinical evidence of dehydration
    - Fludrocortisone 0.1 mg od added



Case 2

- **Treatment (con't):**
  - Autonomic
    - No improvement on fludrocortisone
    - Rivastigmine dose reduced back to 3 mg bid
    - Less fatigue and orthostasis
    - Improved postural vitals
  - Cognitive/neuropsychiatric
    - Rivastigmine 3 mg bid
    - Cognitively, no worsening
    - MMSE = 24/30

ORIGINAL INVESTIGATION

Syncope and Its Consequences in Patients With Dementia Receiving Cholinesterase Inhibitors

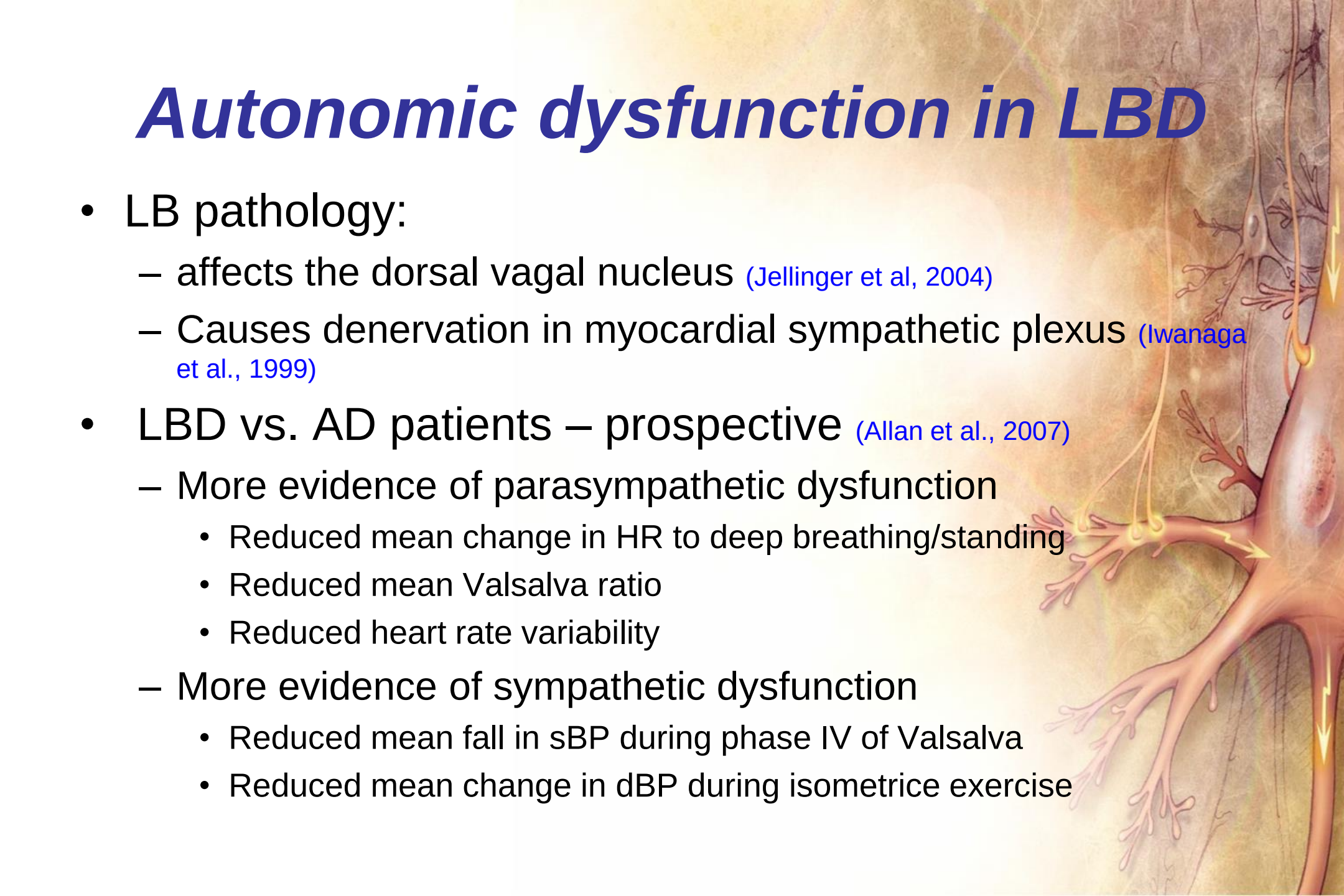
A Population-Based Cohort Study

Arch Intern Med. 2009;169(9):867-873

Sudeep S. Gill, MD, MSc; Geoffrey M. Anderson, MD, PhD; Hadas D. Fischer, MD; Chaim M. Bell, MD, PhD; Ping Li, PhD; Sharon-Lise T. Normand, PhD; Paula A. Rochon, MD, MPH

Autonomic dysfunction in LBD

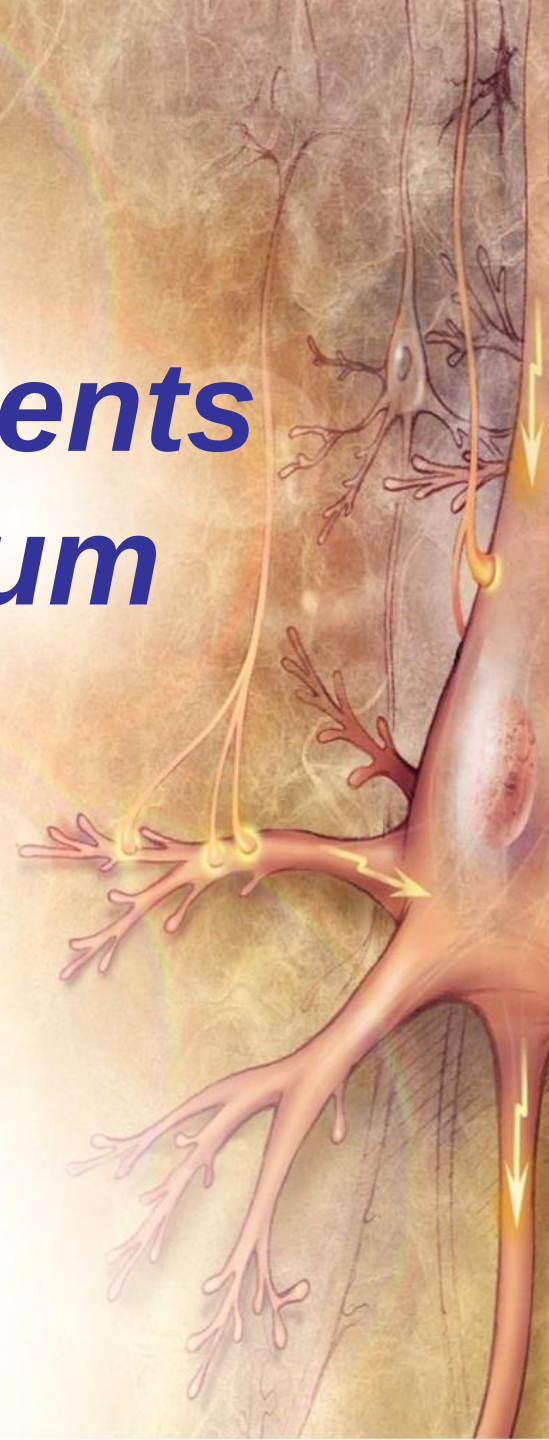
- LB pathology:
  - affects the dorsal vagal nucleus (Jellinger et al, 2004)
  - Causes denervation in myocardial sympathetic plexus (Iwanaga et al., 1999)
- LBD vs. AD patients – prospective (Allan et al., 2007)
  - More evidence of parasympathetic dysfunction
    - Reduced mean change in HR to deep breathing/standing
    - Reduced mean Valsalva ratio
    - Reduced heart rate variability
  - More evidence of sympathetic dysfunction
    - Reduced mean fall in sBP during phase IV of Valsalva
    - Reduced mean change in dBP during isometrice exercise



Treatment of orthostatic hypotension in LBD

- Elastic stockings
- High salt intake
- Head-up tilt
- Fludrocortisone 0.1-0.3 mg od
- Midodrine 2.5-10 mg/daily – tid

Up and coming treatments in Lewy body spectrum disorders



Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial

Lancet Neurol 2009; 8: 613–18

Dag Aarsland, Clive Ballard, Zuzana Walker, Fredrik Bostrom, Guido Alves, Katja Kossakowski, Iracema Leroi, Francisco Pozo-Rodriguez, Lennart Minthon, Elisabet Londos

Conclusions

- DLB and PDD are common and cause significant disability and mortality
- Deficits in cholinergic transmission are thought to underlie cognitive and neuropsychiatric symptoms
- Cholinesterase inhibitors are the mainstay of pharmacological treatment of cognitive and neuropsychiatric symptoms