Disclosures

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- Consultant, Bioscape Medical Imaging CRO

The Spectrum of Lewy Body Disease: Dementia with Lewy Bodies and Parkinson's Disease Dementia

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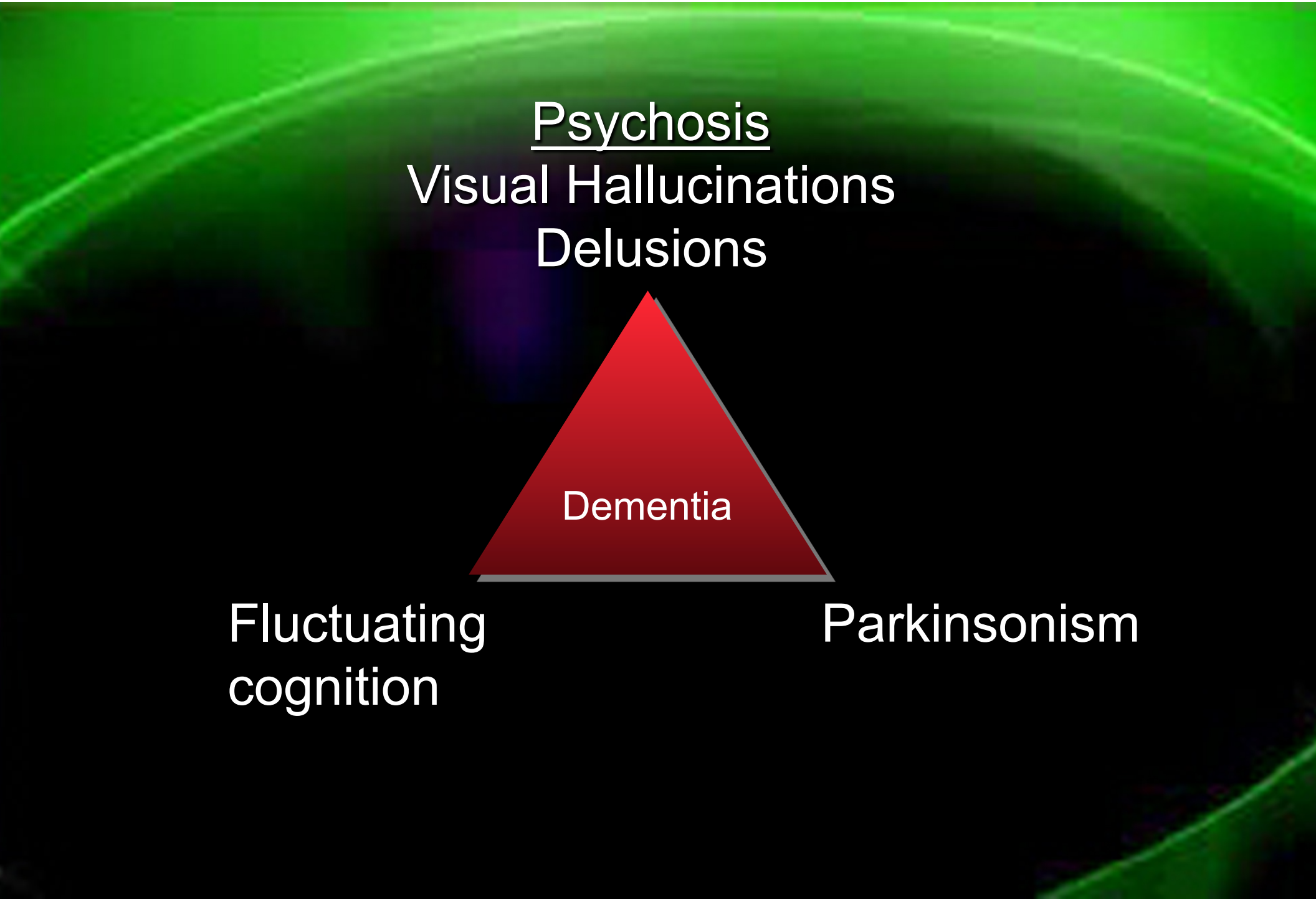
Objectives

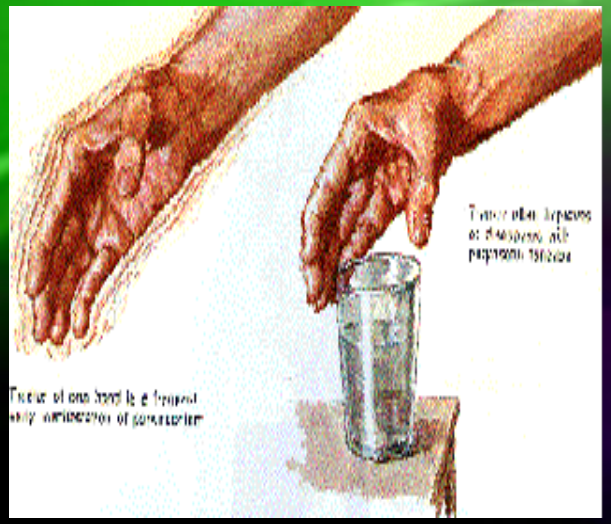
1. To briefly review features of Dementia with Lewy bodies and related conditions
2. To review the underlying brain changes and chemistry of Lewy body disease
3. To provide an overview of treatment strategies in Lewy body disease with a focus on behaviour and thinking


Psychosis
Visual Hallucinations
Delusions
Dementia
Fluctuating cognition
Parkinsonism

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 movement
- Parkinson's Disease – LATE – troubles with dementia and visual hallucinations; therefore, Parkinson's Disease with dementia
- Dementia with Lewy bodies – EARLY – troubles with movement, dementia and visual hallucinations

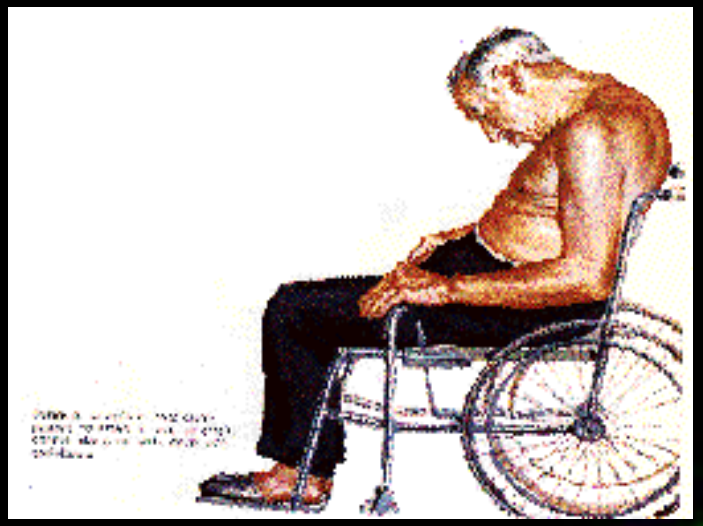
Parkinson’s Disease



First signs -Resting tremor

Stooped, shuffling gait

Rigidity



Late stage - Immobility

T Tremor (unilateral, resting)

R Rigidity

A Akinesia/Bradykinesia

P Postural Δs (slouched, hunched over)

D Depression
Dementia (Lewy Body)

M Mask like faces

E Eyes have ↓ blink rate

D Dysphagia, Drooling, Dysphonia, DREAMS

G Gait (festination, falls, block turn, freezing)

A Arm Swing ↓

M Micrographia

E Eyes (Glabellar)

S Seborrhea

O Orthostatic Hypotension

Idiopathic Parkinson's Disease

Panel 1: **Clinical diagnostic criteria for idiopathic Parkinson's disease**[19,20]

Clinically possible

One of:

- Asymmetric resting tremor
- Asymmetric rigidity
- Asymmetric bradykinesia

Clinically probable

Any two of:

- Asymmetric resting tremor
- Asymmetric rigidity
- Asymmetric bradykinesia

Clinically definite

- Criteria for clinically probable
- Definitive response to anti parkinson drugs

Ward et al. (1990); Calne et al. (1992)

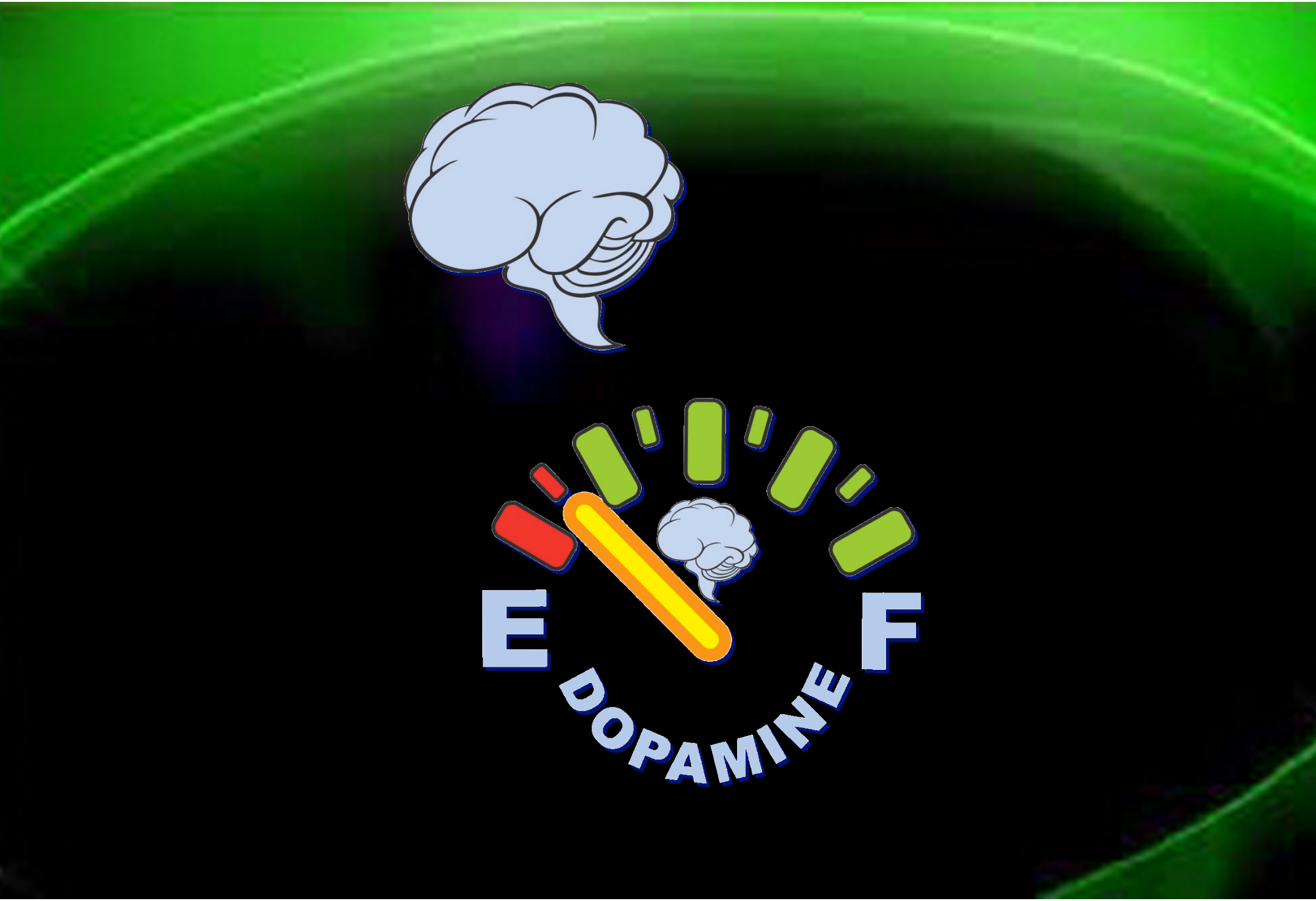
Epidemiology of PD

- Affects about 100,000 Canadians
- Prevalence over age 60 ≈ 1%
- In Ontario, > 90% of patients over age 60
- Typical age of onset ranges from 40 to 70
- Mean age of onset = early to mid-60s

(Guttman et al., 2003; Samii et al., 2004)

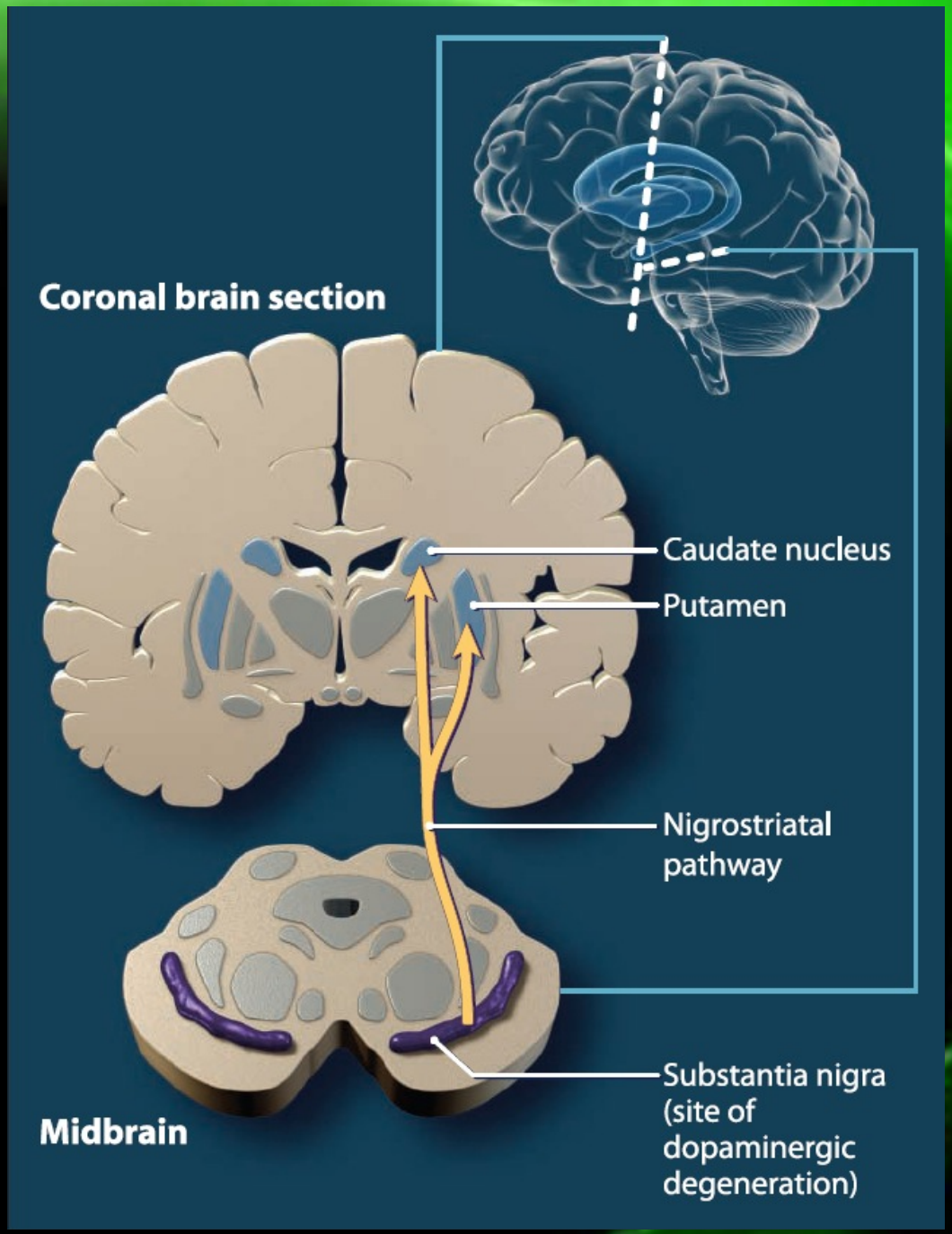
Atypical Features

- 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


E
DOPAMINE
F

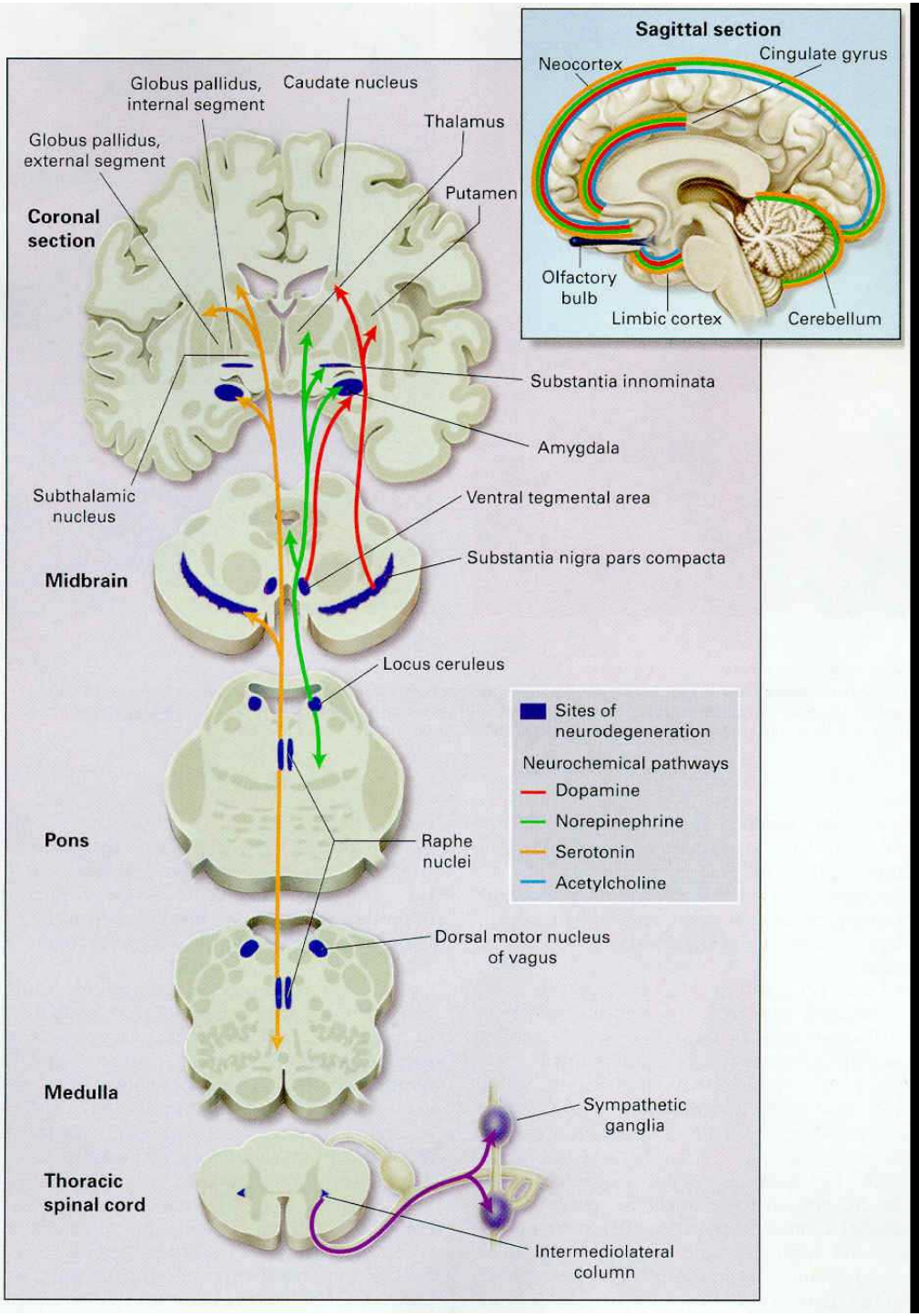
Pathophysiology of motor symptoms

(Guttman et al., 2003)



More than just dopamine….

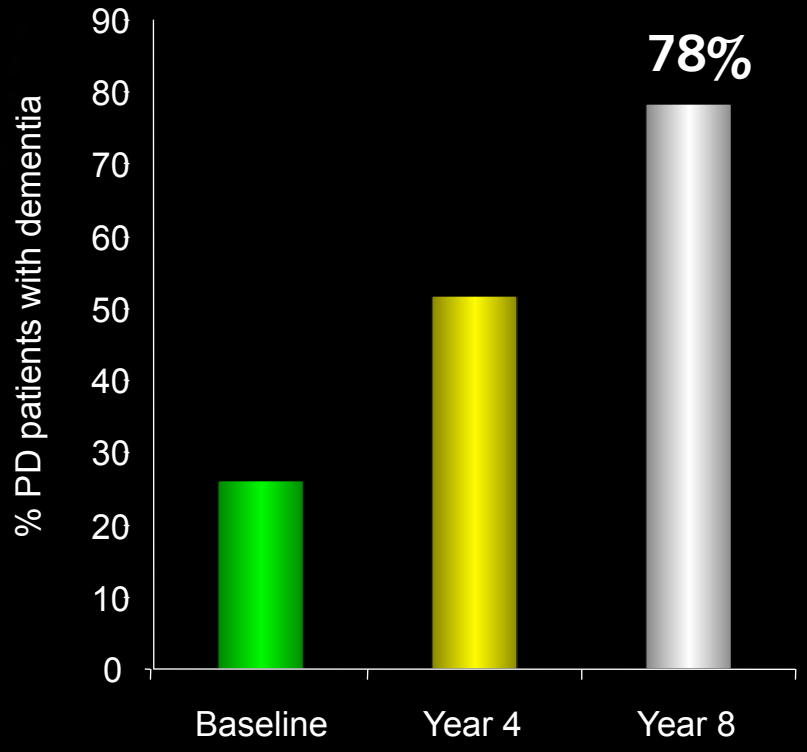
(Lang & Lozano, 1998)



Parkinson’s disease with dementia

Epidemiology of PD Dementia

- 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

Diagnosing PD 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

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

Dementia with Lewy bodies

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)

Bottom Line

- Together DLB and PDD account for ~ 20% of all cases of dementia

Diagnosing Dementia with Lewy bodies

- Central feature
  - dementia
- Core features
  - Fluctuating cognition and alertness
  - Recurrent visual hallucinations
  - Spontaneous Parkinsonism
- Suggestive features
  - REM sleep behavioural disorder
  - Severe neuroleptic sensitivity

Clinical Overlap in DLB and PDD

Cognitive ('visual-perceptive and attentional-executive dementia')

- Impaired executive function and attention with fluctuations
- Bradyphrenia, impaired memory (retrieval)
- Impaired visuospatial function
- Impaired verbal fluency (Collerton et al., 2003)

Neuropsychiatric

- Personality changes
- Mood and behavioural symptoms (apathy, depression, visual hallucinations)

Motor

- Spontaneous Parkinsonism

→ Less able to function independently in daily life

(Emre, 2003; Gelb et al., 1999)

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**

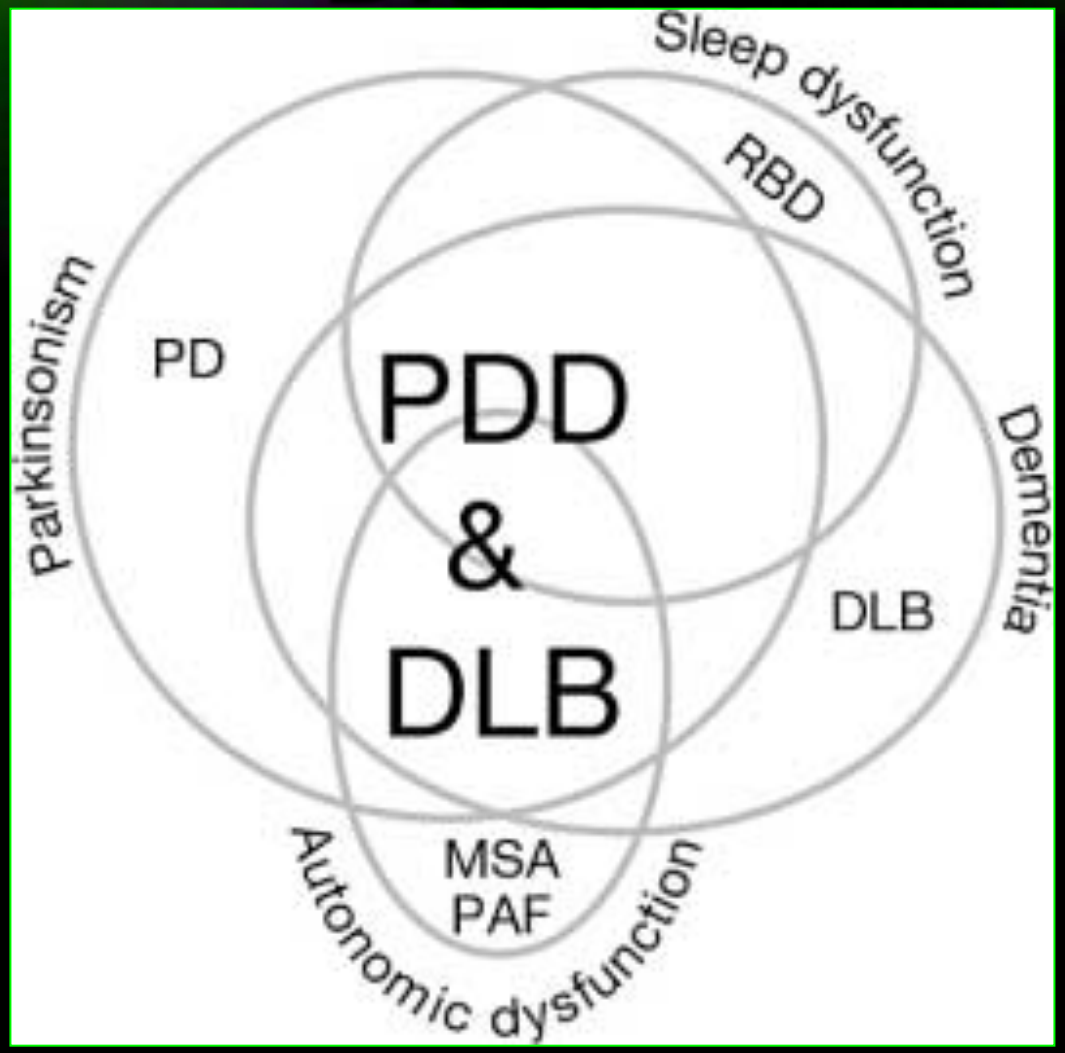
~ 20% of all dementia cases

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

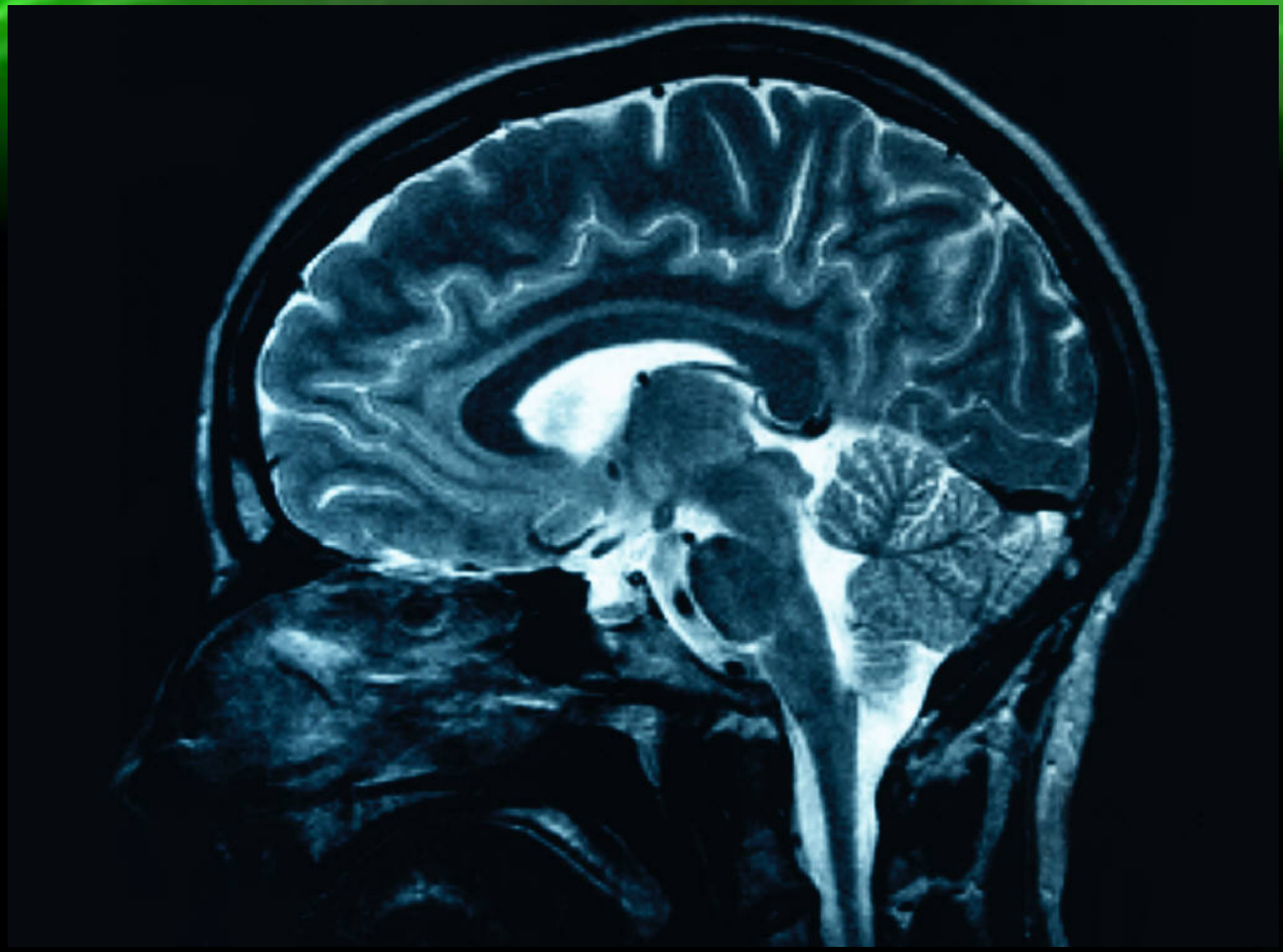
Distinguishing Features of Different Dementia Types

- Alzheimer's Disease (AD)
  - Apathy
  - Impairment of memory (storage) significantly interference with activities of daily life
- Dementia associated with PD
  - Apathy
  - Fluctuating impairment of attention/executive function and memory (retrieval) significantly interfering with activities of daily life
- Dementia with Lewy Bodies
  - Fluctuating cognition with pronounced variation in attention and alertness
  - Recurrent visual hallucinations, typically well formed and detailed
  - Spontaneous motor features of parkinsonism

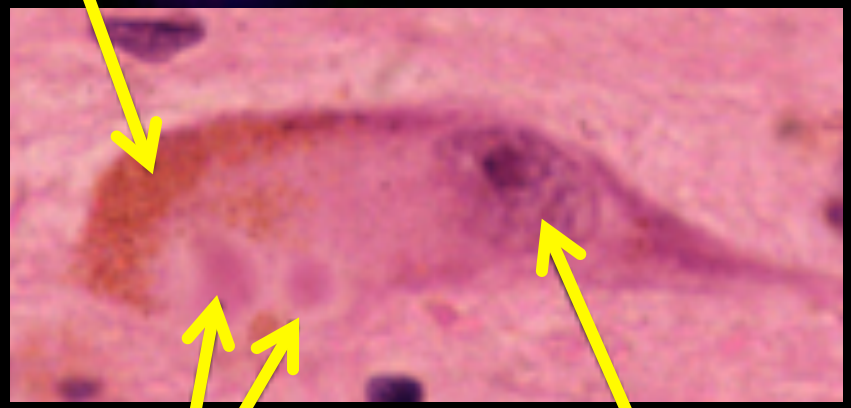
Spectrum of Lewy Body Disease



Duda, 2004

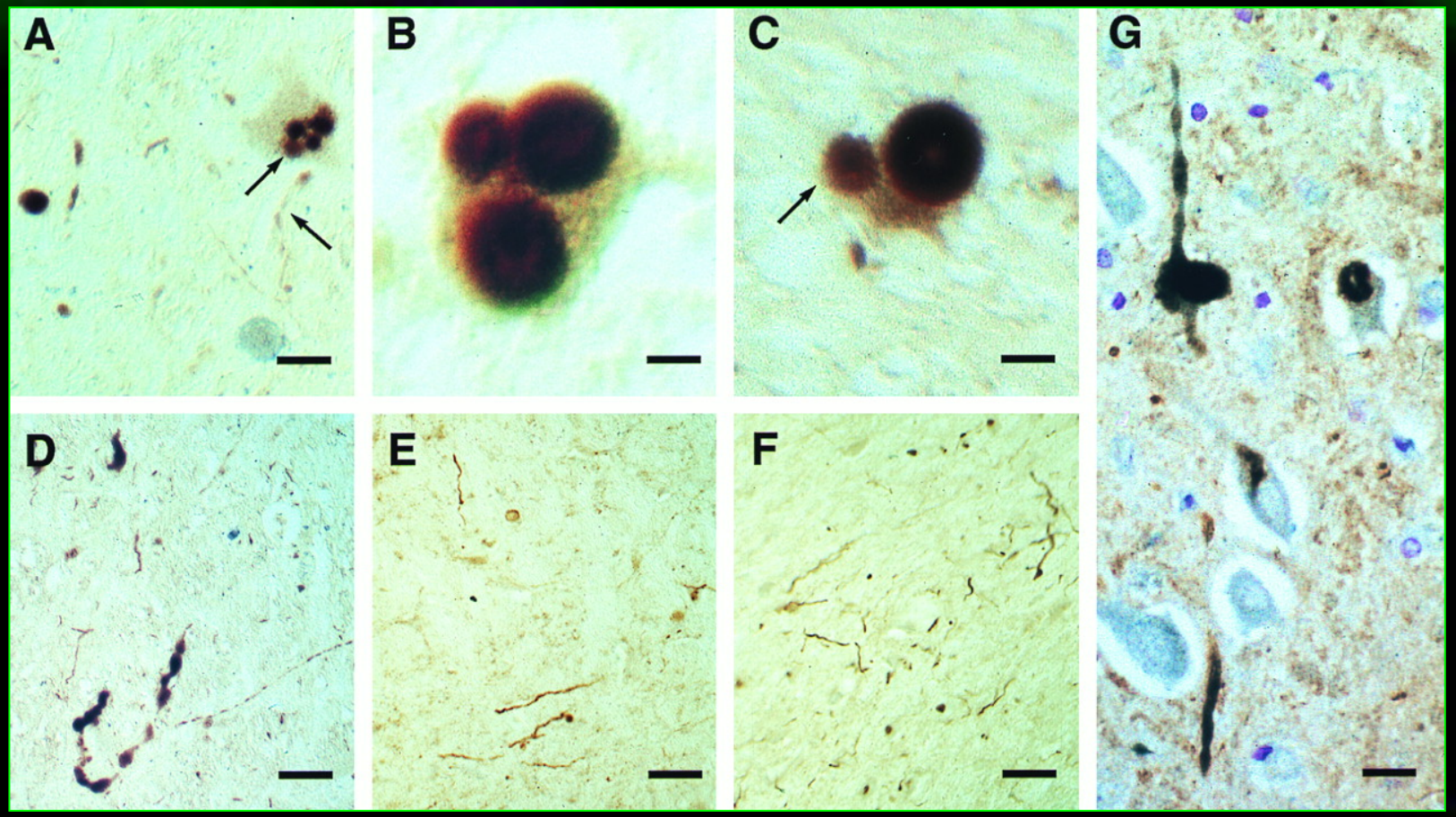


Common Lewy Body Pathology: α-synuclein



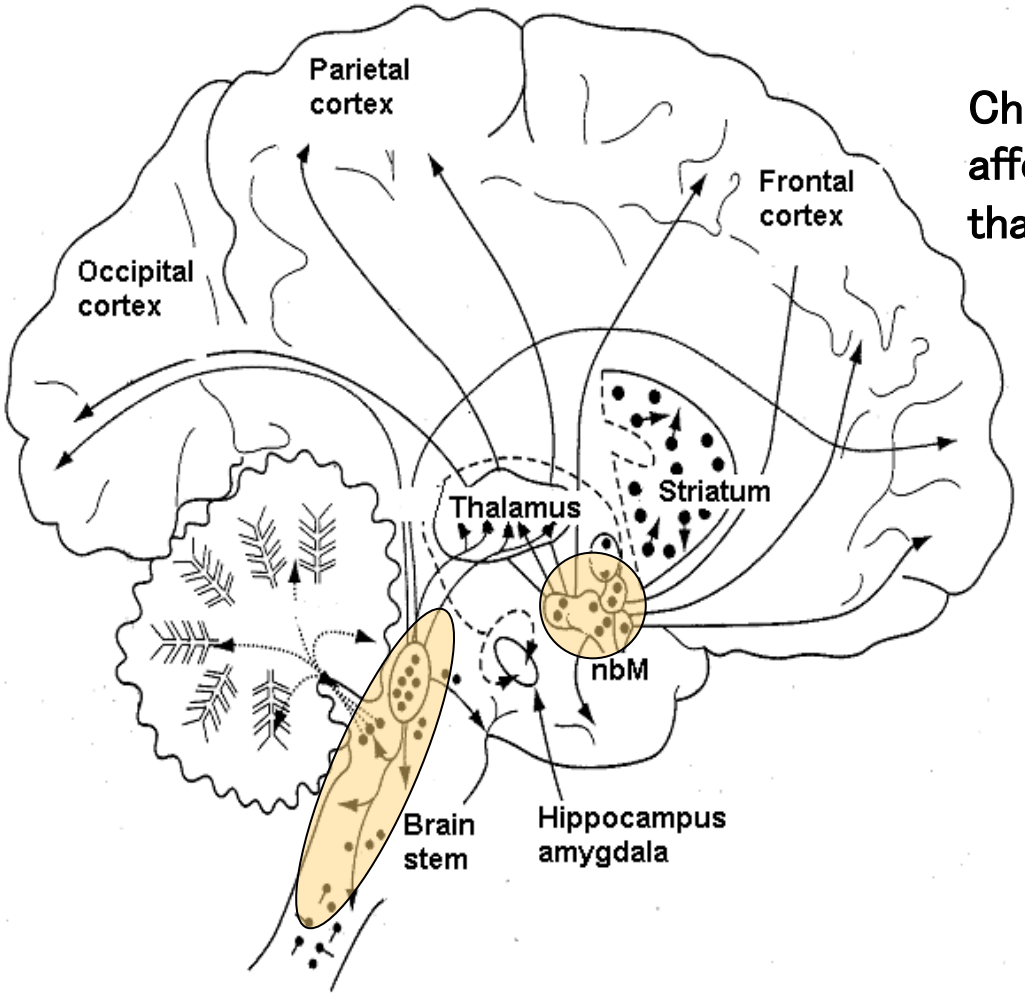
Esiri MM, McShane RH. *Cambridge University Press* 1997
Gelb DJ. *Arch Neurol* 1999;56:33–9

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

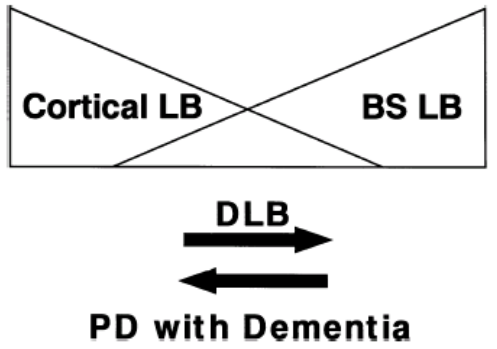


Spillantini et al., 1998

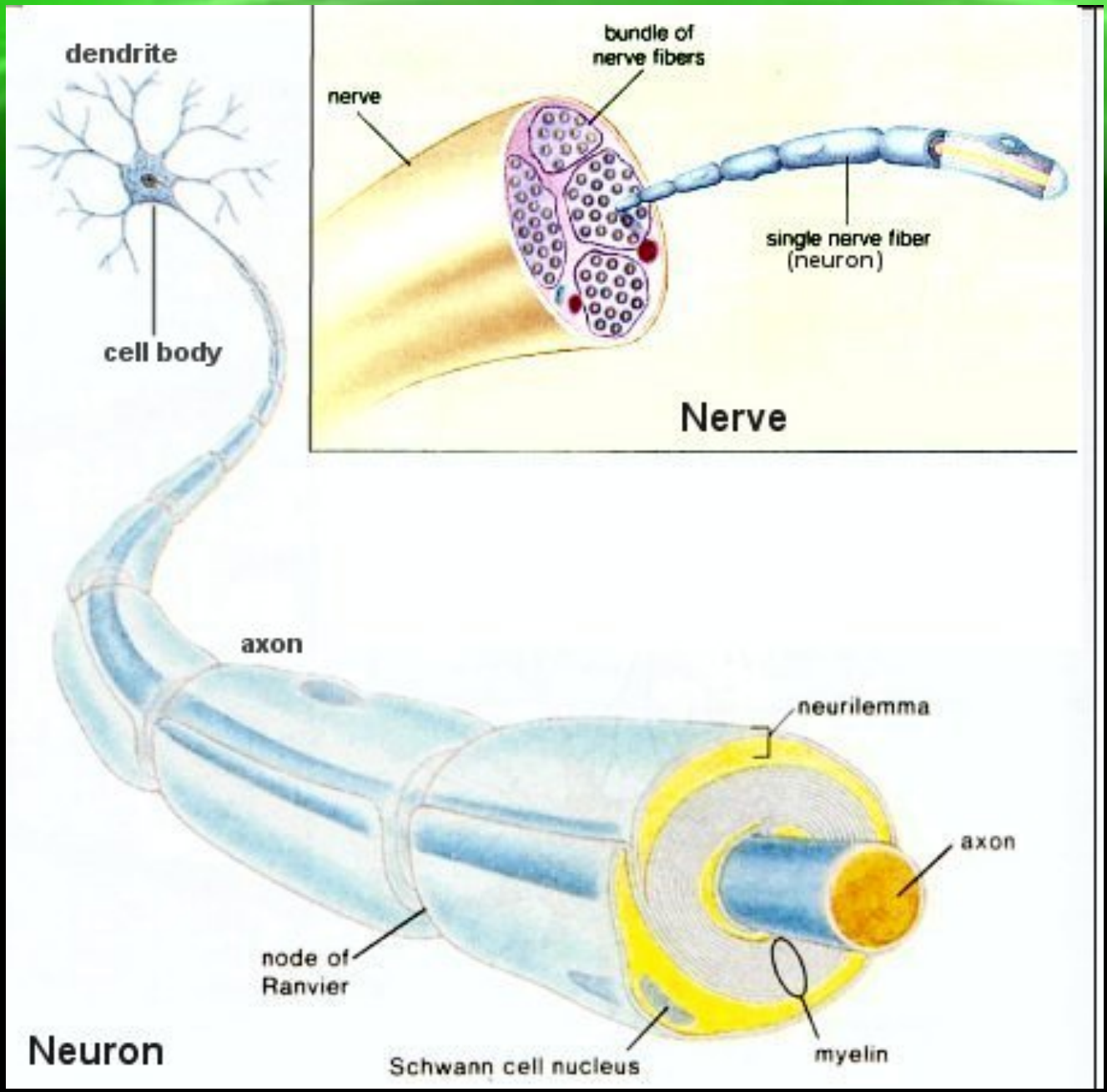
Neurochemistry of DLB and PDD



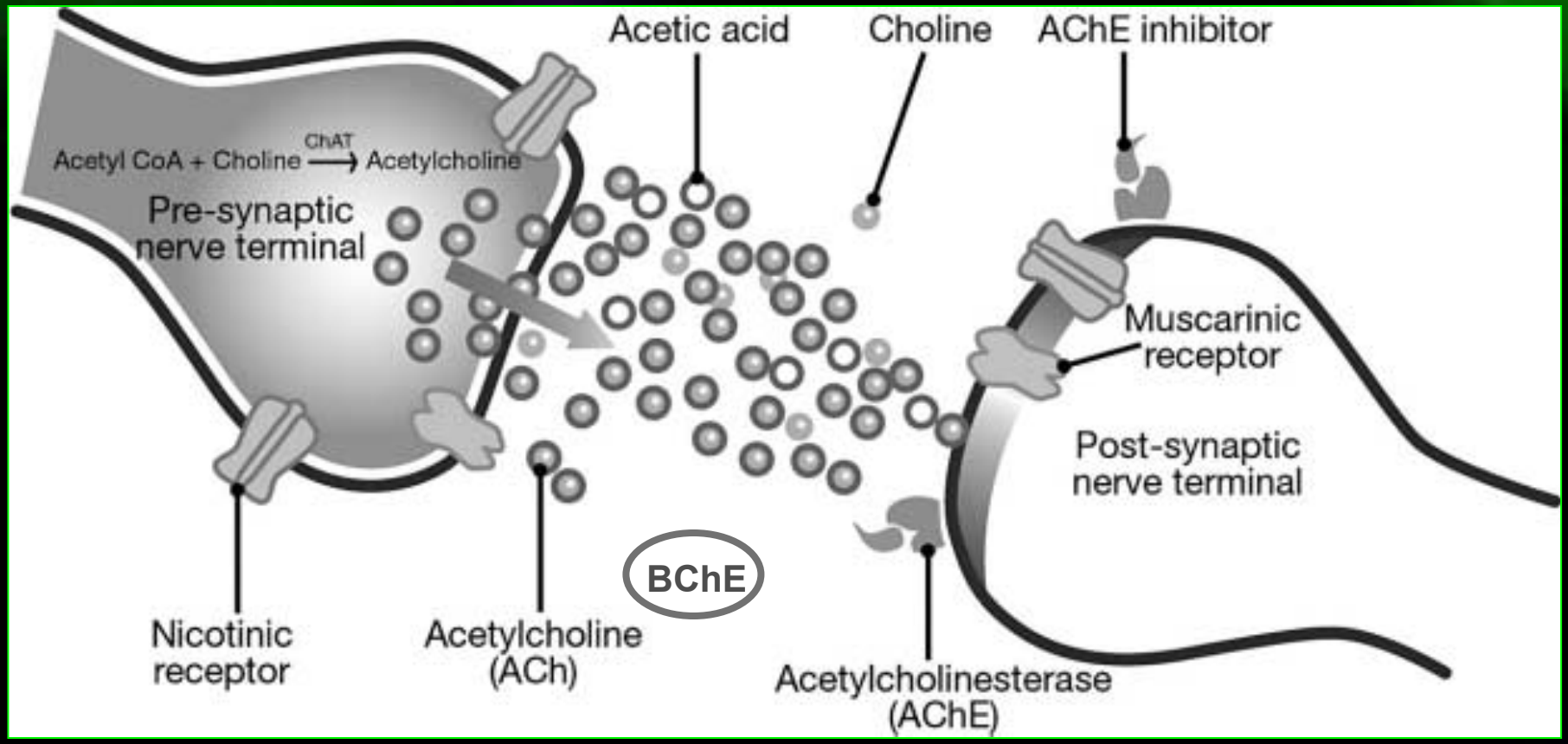
Cholinergic loss in PDD and DLB affects frontostriatal–thalamocortical circuits



Perry et al., 1999; Mori, 2002

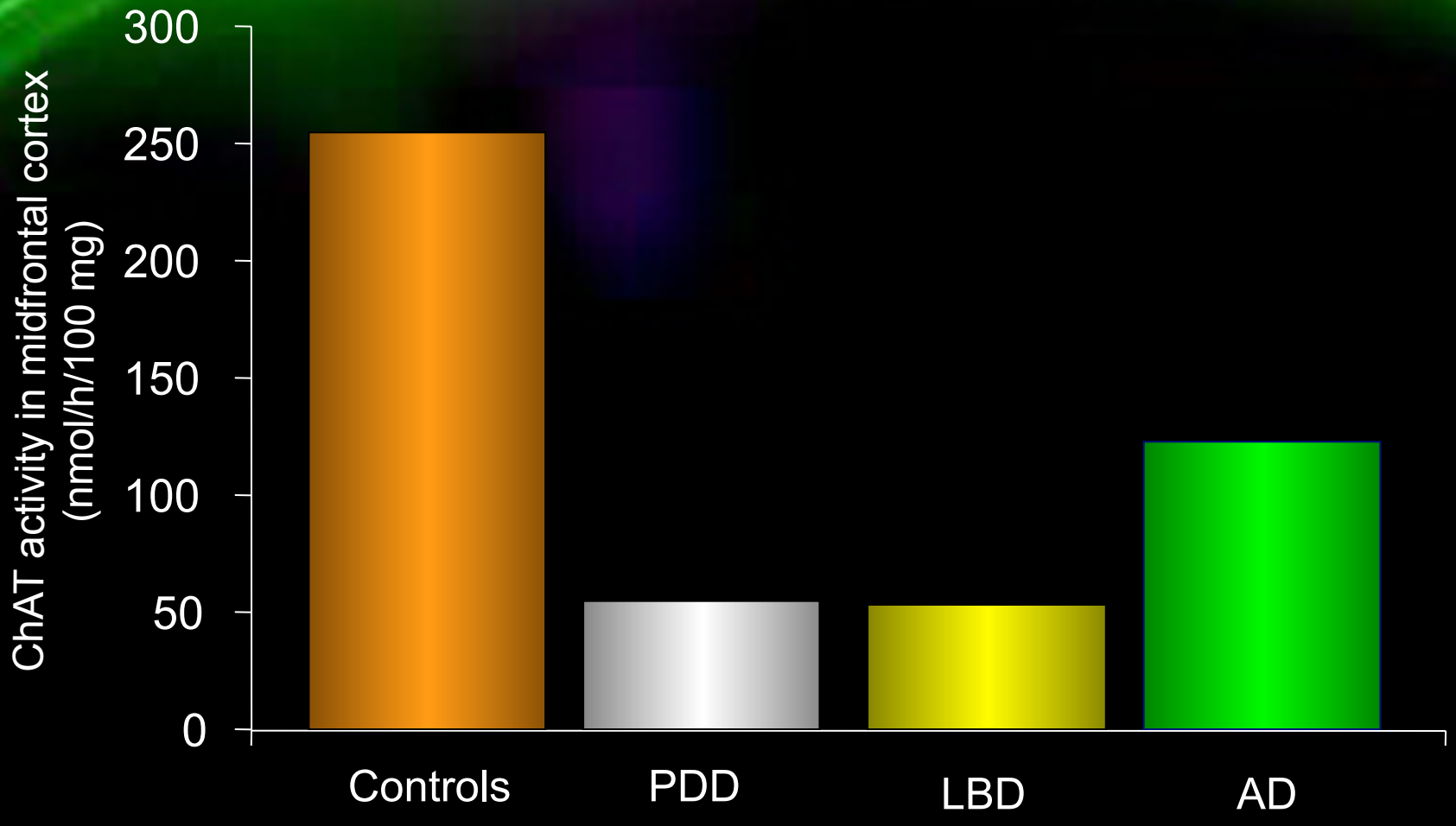

dendrite
cell body
bundle of
nerve fibers
nerve
single nerve fiber
(neuron)
Nerve
axon
neurilemma
axon
node of
Ranvier
Schwann cell nucleus
myelin
Neuron

Cholinergic synapse



Duda, 2004

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

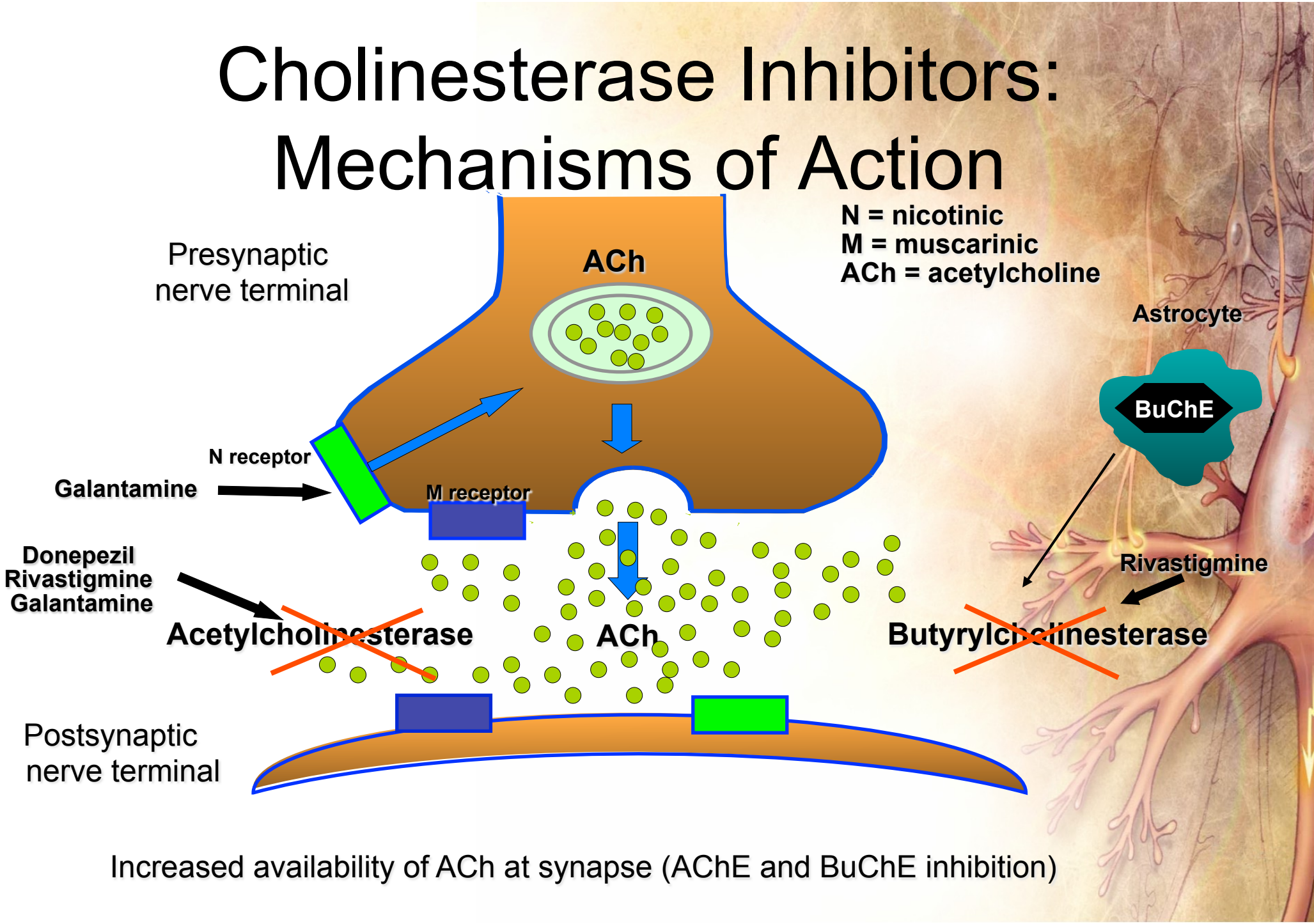
The Challenge of Treating the Symptoms of PDD and DLB

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

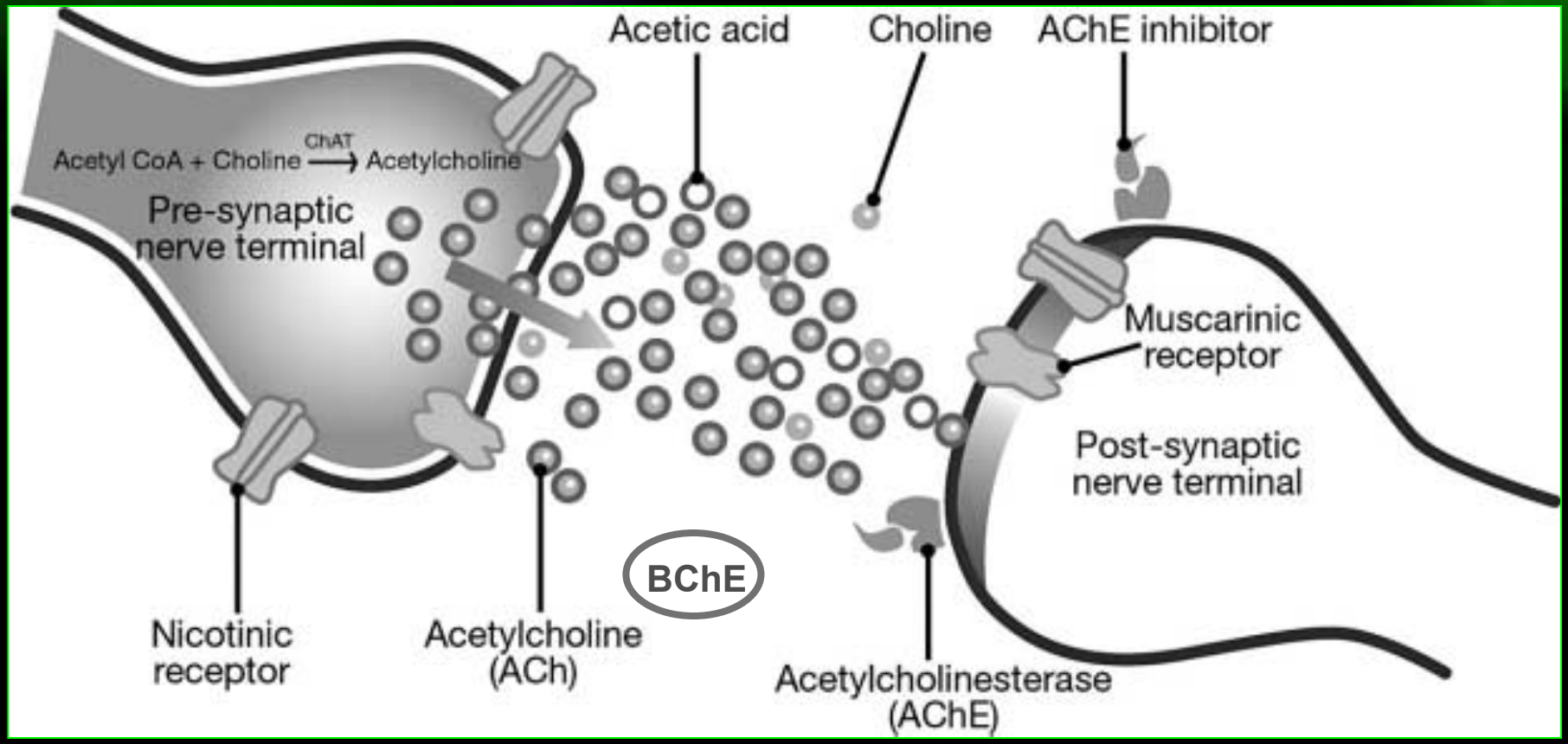
Cholinesterase Inhibitors: Mechanisms of Action



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

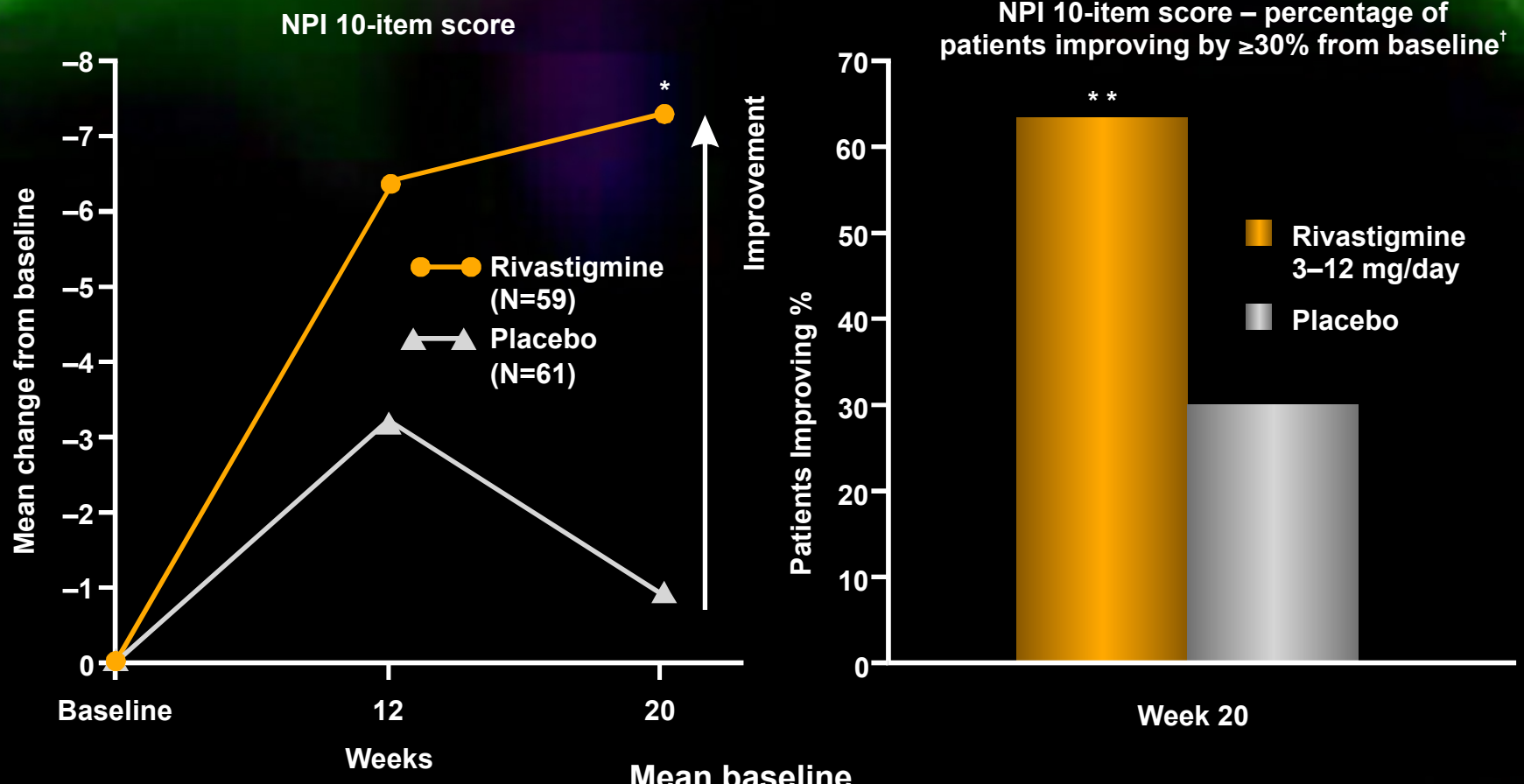
Treatment in DLB and PDD: Cholinesterase Inhibitors

(Donepezil, rivastigmine, and galantamine)



Duda, 2004

Efficacy of rivastigmine on neuropsychiatric symptoms in DLB



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

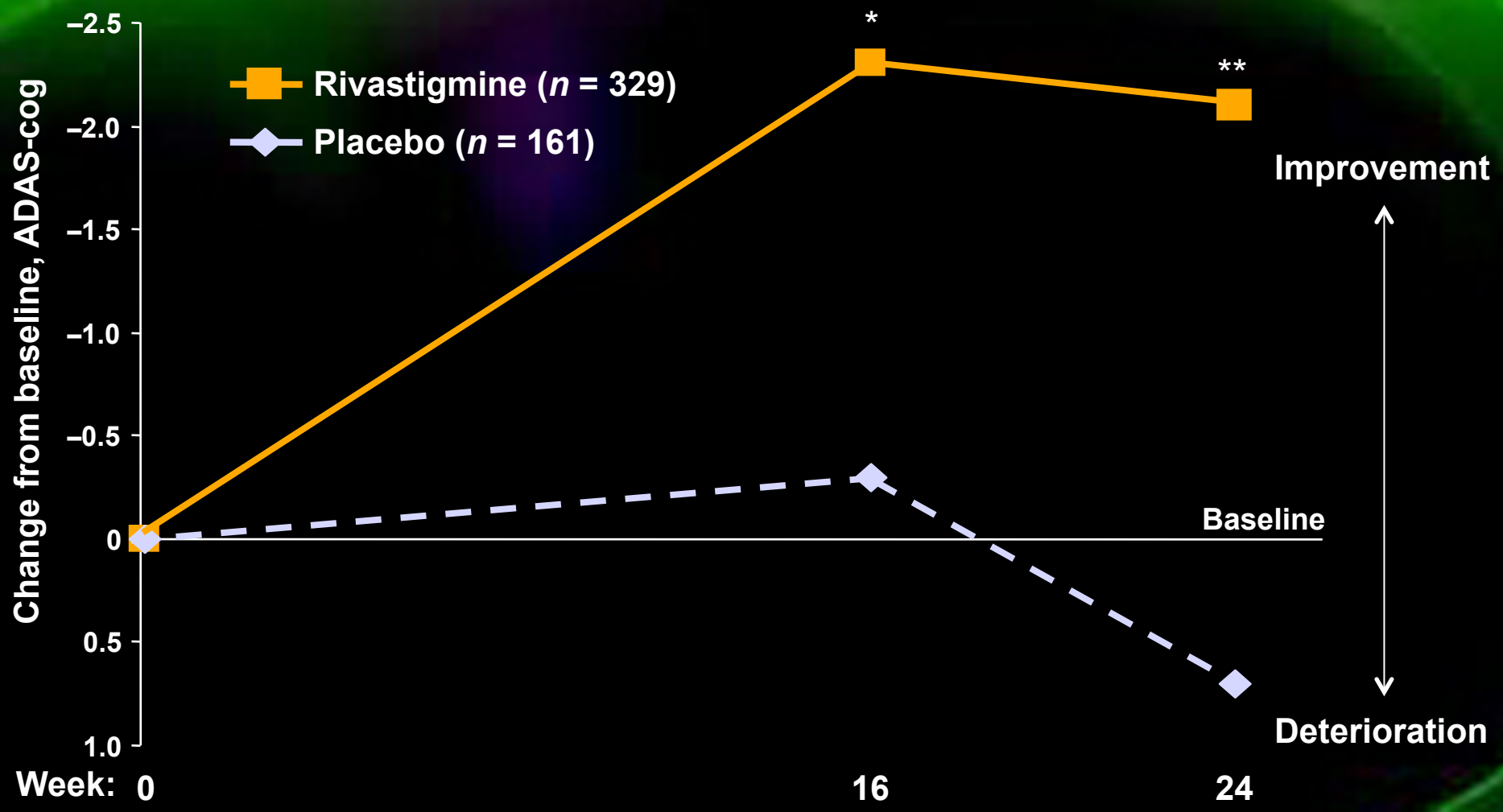
OC analysis

*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

Conclusions

- DLB and PDD occur along a spectrum of Lewy Body Disease
- DLB and PDD are common and cause significant disability and mortality
- Deficits in cholinergic transmission secondary to Lewy body pathology are thought to underlie cognitive symptoms
- More than just acetylcholine
- Multimodal approach to treatment
- Cholinesterase inhibitors are the mainstay of pharmacological treatment of cognitive and psychiatric symptoms