Sleep Disorders Pertinent to Dementia Research: REM Sleep Behavior Disorder and Obstructive Sleep Apnea

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Disclosures

Financial/Other

- Investigator for a clinical trial sponsored by GE Healthcare
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- Advisor for the Tau Consortium
- Honoraria from the American Academy of Neurology
- Research support from the NIA, NINDS, Alzheimer's Association, Mangurian Foundation

Off-label and/or Investigational Use

- May discuss use of some medications and/or devices not FDA-approved for the indications to be reviewed

Sleep Disorders Pertinent to Dementia Research: REM Sleep Behavior Disorder and Obstructive Sleep Apnea

Objectives

REM Sleep Behavior Disorder (RBD)

- To review the clinical features and pathophysiology of RBD
- To review the relevance of RBD to dementia research

Obstructive Sleep Apnea (OSA)

- To review the clinical features and pathophysiology of OSA
- To review the relevance of OSA to dementia research

ADC Program/NACC

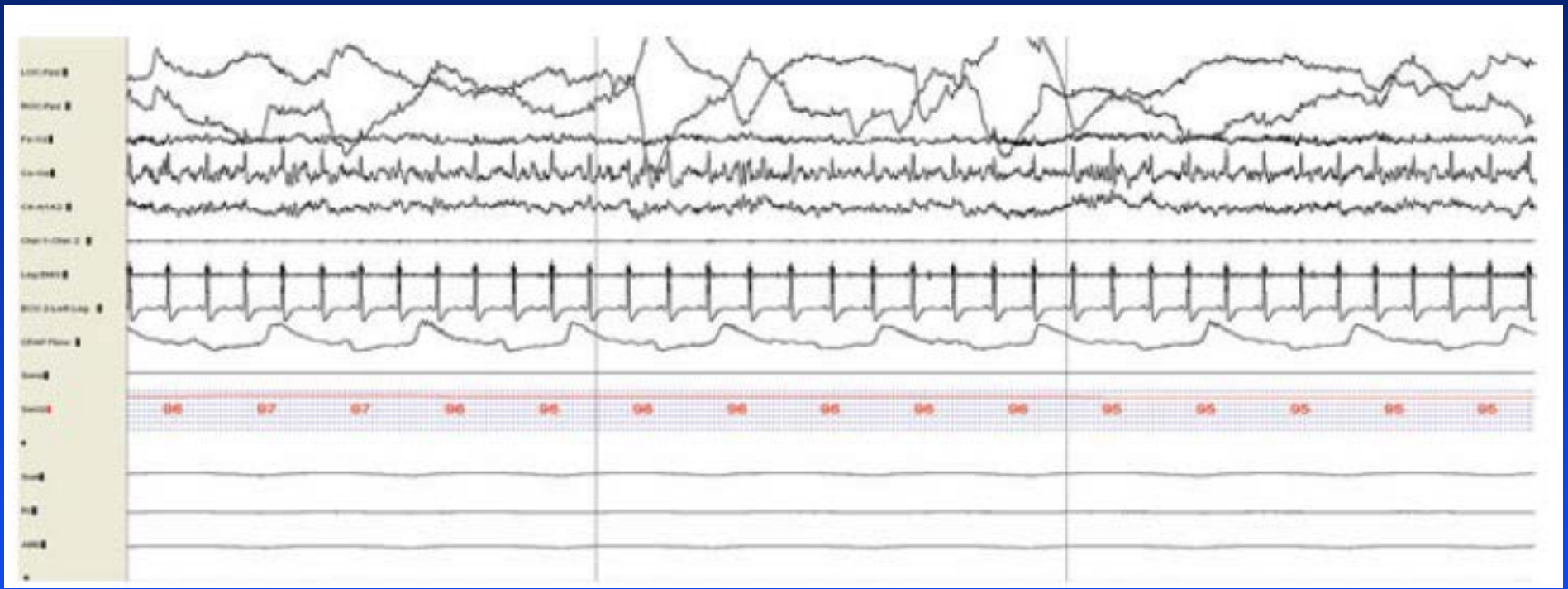
- To underscore the importance of recording sleep-related issues in UDS 3.0

REM Sleep Behavior Disorder

States of Being

- Wakefulness
- Non-REM Sleep
  - Stage N1
  - Stage N2
  - Stage N3
- REM sleep (Stage R)

Normal REM Sleep



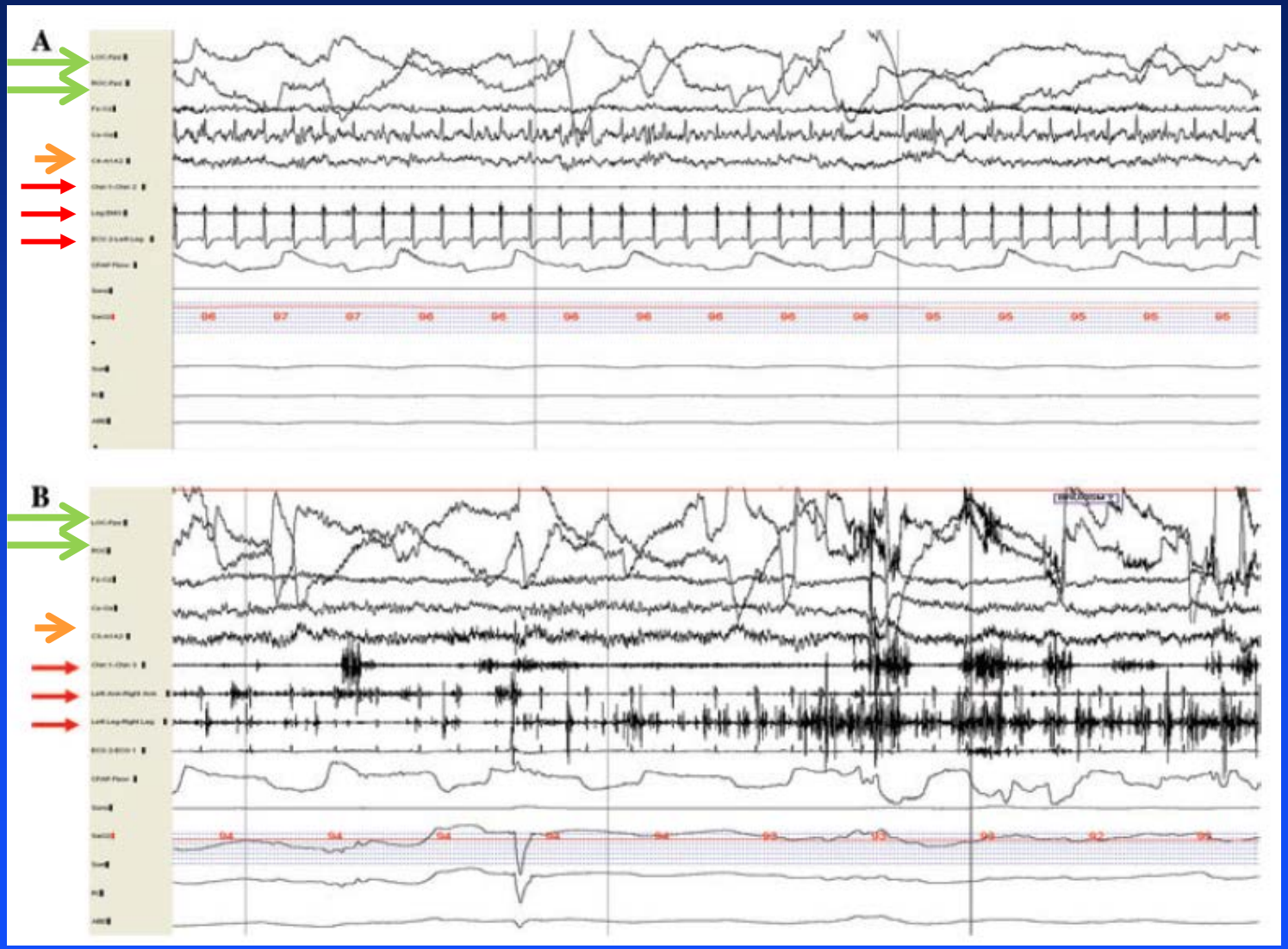
Normal REM Sleep

REM Sleep Behavior Disorder

Clinical Features

- Simple or complex limb movements and/or vocalizations during rapid eye movement (REM) sleep
- Behaviors typically mirror the content of the dream when a patient is awakened and questioned
- Dream content often involves animals and/or people with chasing or attacking theme
- Behaviors can be violent, and patient and bedpartner injuries can occur

Normal REM Sleep vs REM Sleep Without Atonia

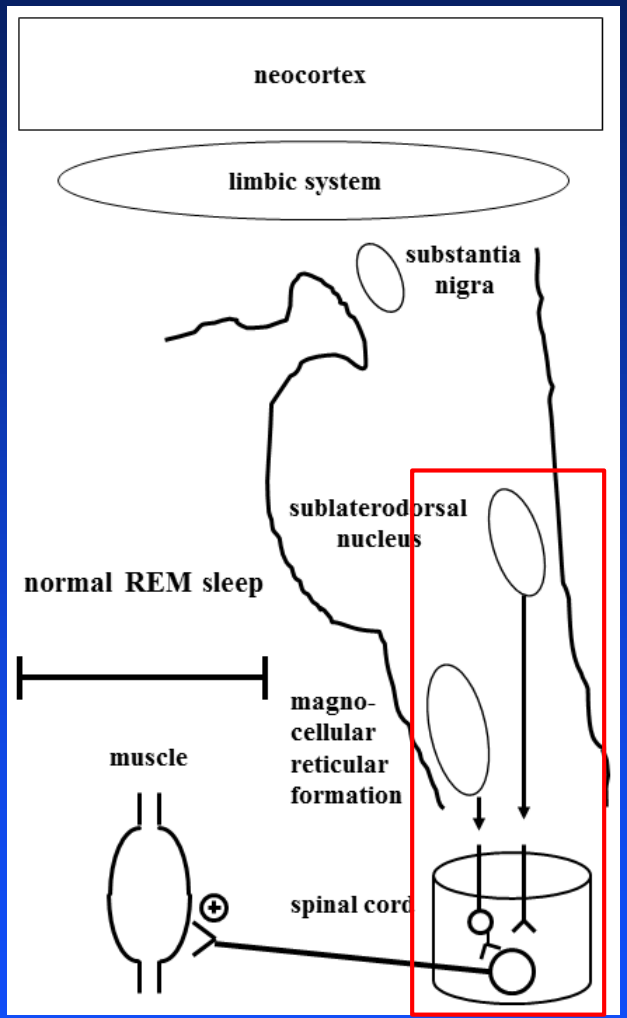


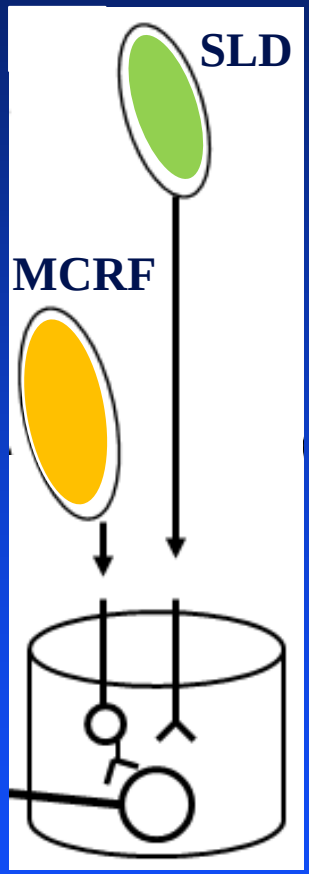
Normal REM Sleep

REM Sleep Without Atonia (RSWA)

REM Sleep Behavior Disorder

RBD Pathophysiology



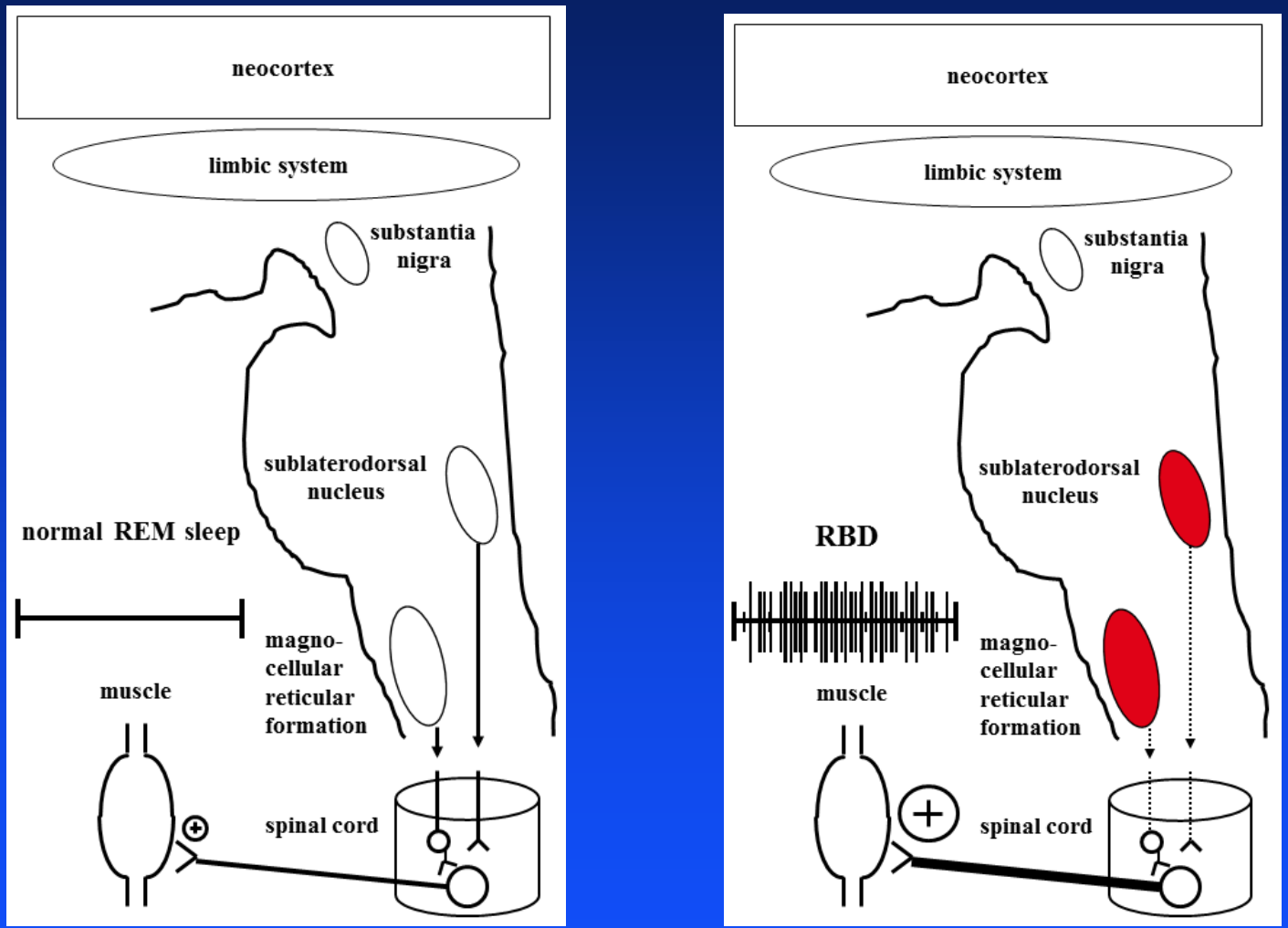


Gly
GABA

Glu

Adapted from Boeve BF, Lancet Neurol 2013

RBD Pathophysiology

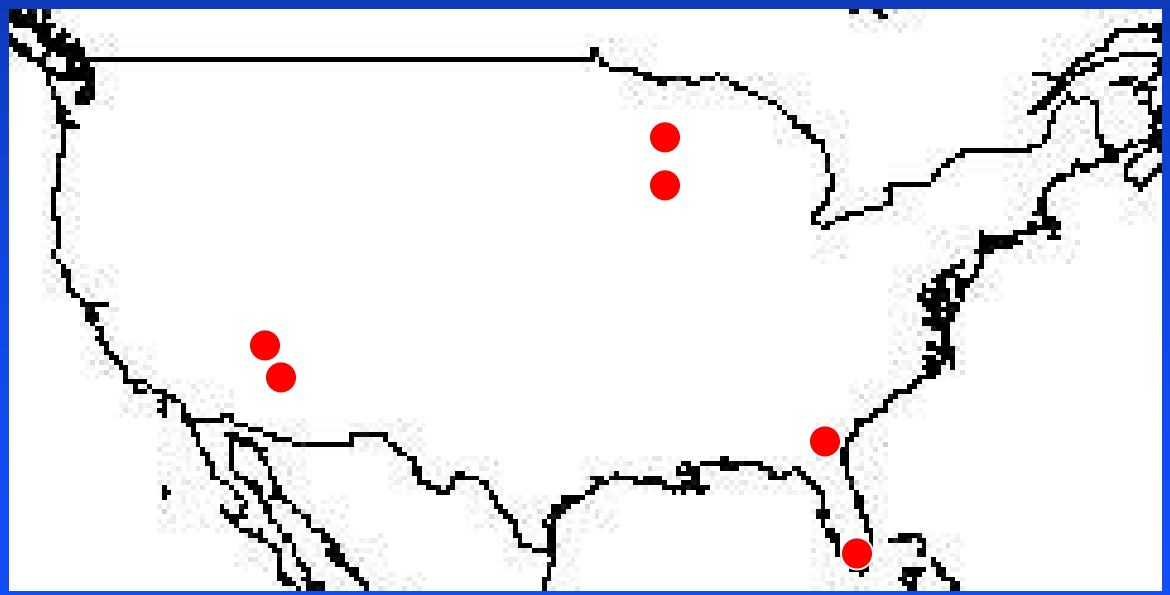


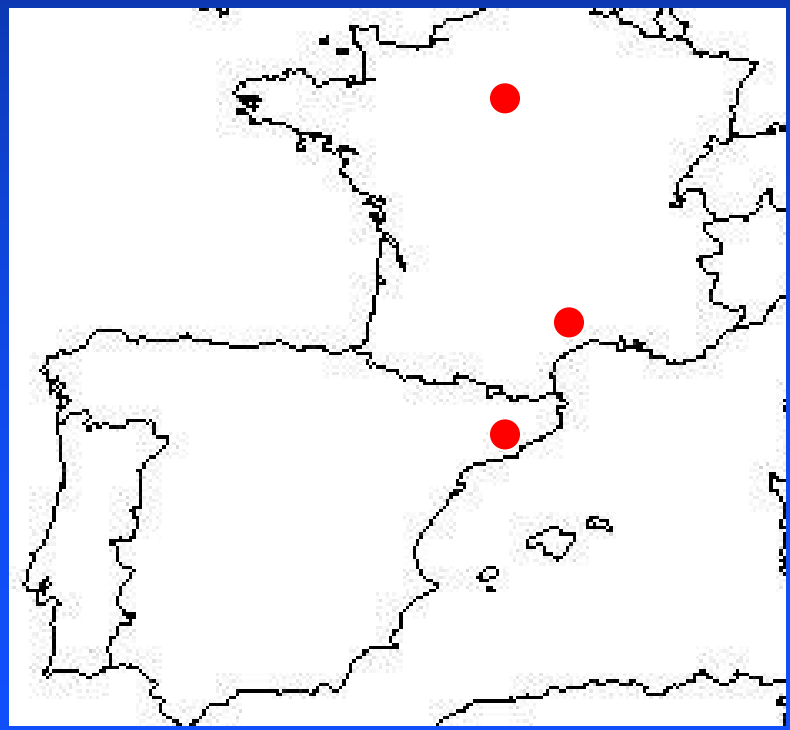
Adapted from Boeve BF, Lancet Neurol 2013

RBD is Associated with the Synucleinopathies

Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder

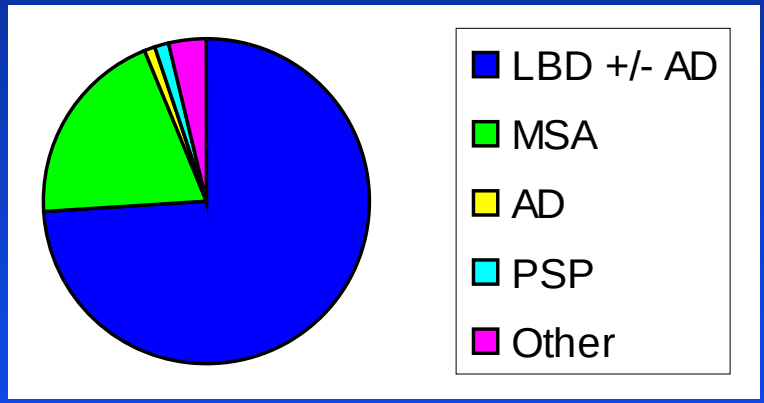
B.F. Boeve [a,b,*], M.H. Silber [a,b], T.J. Ferman [g], S.C. Lin [d,g], E.E. Benarroch [a], A.M. Schmeichel [a], J.E. Ahlskog [a], R.J. Caselli [h], S. Jacobson [i], M. Sabbagh [i], C. Adler [h], B. Woodruff [h], T.G. Beach [i], A. Iranzo [l], E. Gelpi [l], J. Santamaria [l], E. Tolosa [l], C. Singer [k], D.C. Mash [k], C. Luca [k], I. Arnulf [m], C. Duyckaerts [m], C.H. Schenck [j], M.W. Mahowald [j], Y. Dauvilliers [n], N.R. Graff-Radford [c], Z.K. Wszolek [c], J.E. Parisi [a,e], B. Dugger [i], M.E. Murray [f], D.W. Dickson [f]





RBD is Associated with the Synucleinopathies – Which is Typically Lewy Body Disease

Primary Neuropathologic Diagnosis	PSG-confirmed n=82 (%)
Neurodegenerative/Prion	
Lewy body disease +/- Alzheimer's disease	59 (72)
Lewy body disease*	34 (41)
Combined LBD and AD	25 (30)
Multiple system atrophy	16 (20)
Alzheimer's disease	1 (1)
Progressive supranuclear palsy	1 (1)
Other	3(4)
Combined LBD and MSA	2
Combined LBD and ALS	1
NBIA-1 + LBD + tauopathy	0
CJD and ALS	0
Indeterminate degenerative	0
Synucleinopathy among neurodegenerative diseases	78/80=98%



Boeve BF et al, Sleep Med 2013

RBD Associated with Neurodegenerative Disease

Synucleinopathy
Lewy Body Disease
- Parkinson's disease (PD)
- Dementia with Lewy bodies (DLB)
- Pure autonomic failure (PAF)

Multiple system atrophy (MSA)

Trinucleotide Repeat Disorders
Spinocerebellar Atrophy-3 (SCA-3)
Huntington's Disease (HD)

Prionopathy
Creutzfeldt-Jakob disease (CJD)
Fatal familial insomnia (FFI)
Gerstmann-Straussler-Scheinker (GSS)

Amyloidopathy
Alzheimer's disease (AD)

Tauopathy
Pick's disease
Corticobasal degeneration (CBD)
Progressive supranuclear palsy (PSP)
Argyrophilic grain disease (AGD)
Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17*MAPT*)
Guadeloupean parkinsonism

TDP-43opathy
Frontotemporal lobar degeneration (FTLD) with TDP-43-positive inclusions
FTLD with motor neuron disease (FTLD-MND)
Hippocampal sclerosis (HS)
Amyotrophic lateral sclerosis (ALS)
Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17*PGRN*)

RBD and the Association With Lewy Body Disease/Dementia With Lewy Bodies

HIGH LIGHT

CME

Diagnosis and management of dementia with Lewy bodies

Third report of the DLB consortium

I.G. McKeith, MD, FMedSci; D.W. Dickson, MD; J. Lowe, DM; M. Emre, MD; J.T. O'Brien, DM; H. Feldman, MDCM; J. Cummings, MD; J.E. Duda, MD; C. Lippa, MD; E.K. Perry, DSc; D. Aarsland, MD; H. Arai, MD; C.G. Ballard, MD; B. Boeve, MD; D.J. Burn, FRCP; D. Costa, MD; T. Del Ser, MD, PhD; B. Dubois, MD; D. Galasko, MD; S. Gauthier, MD, FRCPC; C.G. Goetz, MD; E. Gomez-Tortosa, MD, PhD; G. Halliday, PhD; L.A. Hansen, MD; J. Hardy, PhD; T. Iwatsubo, MD; R.N. Kalaria, FRCPath; D. Kaufer, MD; R.A. Kenny, MD; A. Korczyn, MD; K. Kosaka, MD; V.M.-Y. Lee, PhD, MBA; A. Lees, MD; I. Litvan, MD; E. Londos, MD, PhD; O.L. Lopez, MD; S. Minoshima, MD, PhD; Y. Mizuno, MD; J.A. Molina, MD; E.B. Mukaetova-Ladinska, MD, PhD; F. Pasquier, MD, PhD; R.H. Perry, DSc; J.B. Schulz, MD; J.Q. Trojanowski, MD, PhD; and M. Yamada, MD, PhD, for the Consortium on DLB*

McKeith et al, Neurology 2005

RBD and the Association With Lewy Body Disease/Dementia With Lewy Bodies

Table 1 *Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)*

1. *Central feature* (essential for a diagnosis of possible or probable DLB)

   Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. 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 visuospatial ability may be especially prominent.

2. *Core* features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)

   Fluctuating cognition with pronounced variations in attention and alertness

   Recurrent visual hallucinations that are typically well formed and detailed

   Spontaneous features of parkinsonism

3. *Suggestive features* (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)

   REM sleep behavior disorder

   Severe neuroleptic sensitivity

   Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

McKeith et al, Neurology 2005

RBD and the Association With Lewy Body Disease/Dementia With Lewy Bodies

Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies

T.J. Ferman, PhD
B.F. Boeve, MD
G.E. Smith, PhD
S.-C. Lin, MD
M.H. Silber, MBChB
O. Pedraza, PhD
Z. Wszolek, MD
N.R. Graff-Radford, MBBCh, FRCP (London)
R. Uitti, MD
J. Van Gerpen, MD
W. Pao, MD
D. Knopman, MD
V.S. Pankratz, PhD
K. Kantarci, MD
B. Boot, MBBS
J.E. Parisi, MD
B.N. Dugger
H. Fujishiro, MD
R.C. Petersen, MD
D.W. Dickson, MD

Results: Each of the 3 core features increased the odds of autopsy-confirmed DLB up to 2-fold, and RBD increased the odds by 6-fold. When clinically probable DLB reflected dementia and 2 or more of the 3 core features, sensitivity was 85%, and specificity was 73%. When RBD was added and clinically probable DLB reflected 2 or more of 4 features, sensitivity improved to 88%. When dementia and RBD were also designated as probable DLB, sensitivity increased to 90% while specificity remained at 73%. The VH, parkinsonism, RBD model lowered sensitivity to 83%, but improved specificity to 85%.

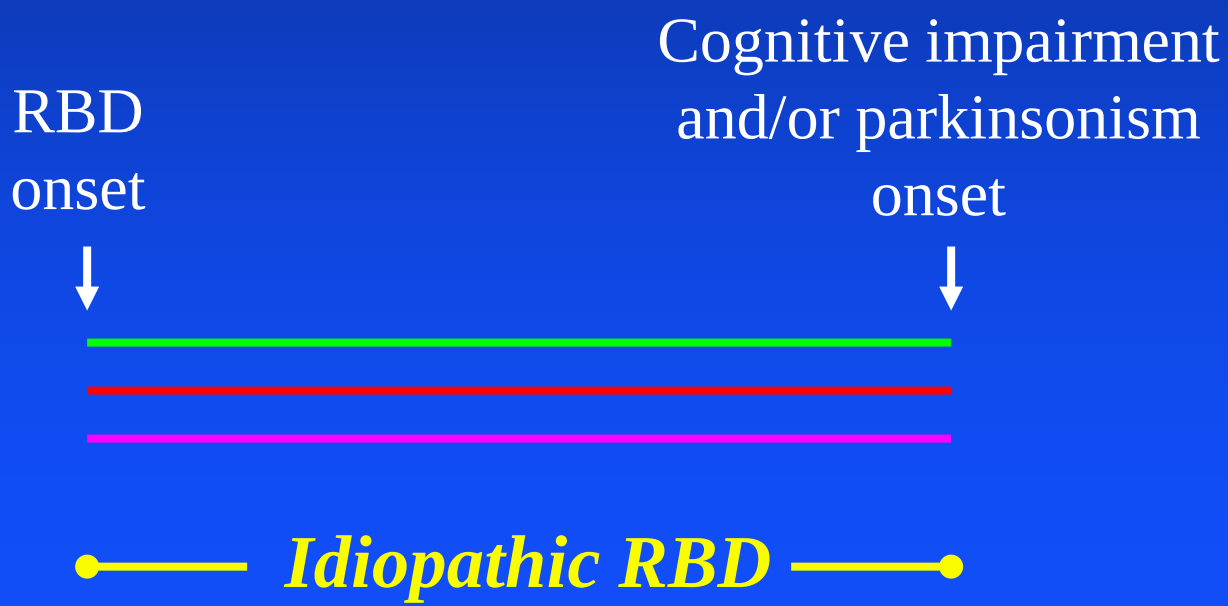
Conclusions: Inclusion of RBD as a core clinical feature improves the diagnostic accuracy of autopsy-confirmed DLB. *Neurology*® 2011;77:875-882

Ferman et al, Neurology 2011

RBD Tends to Precede Cognitive Impairment and/or Parkinsonism by Years or Decades

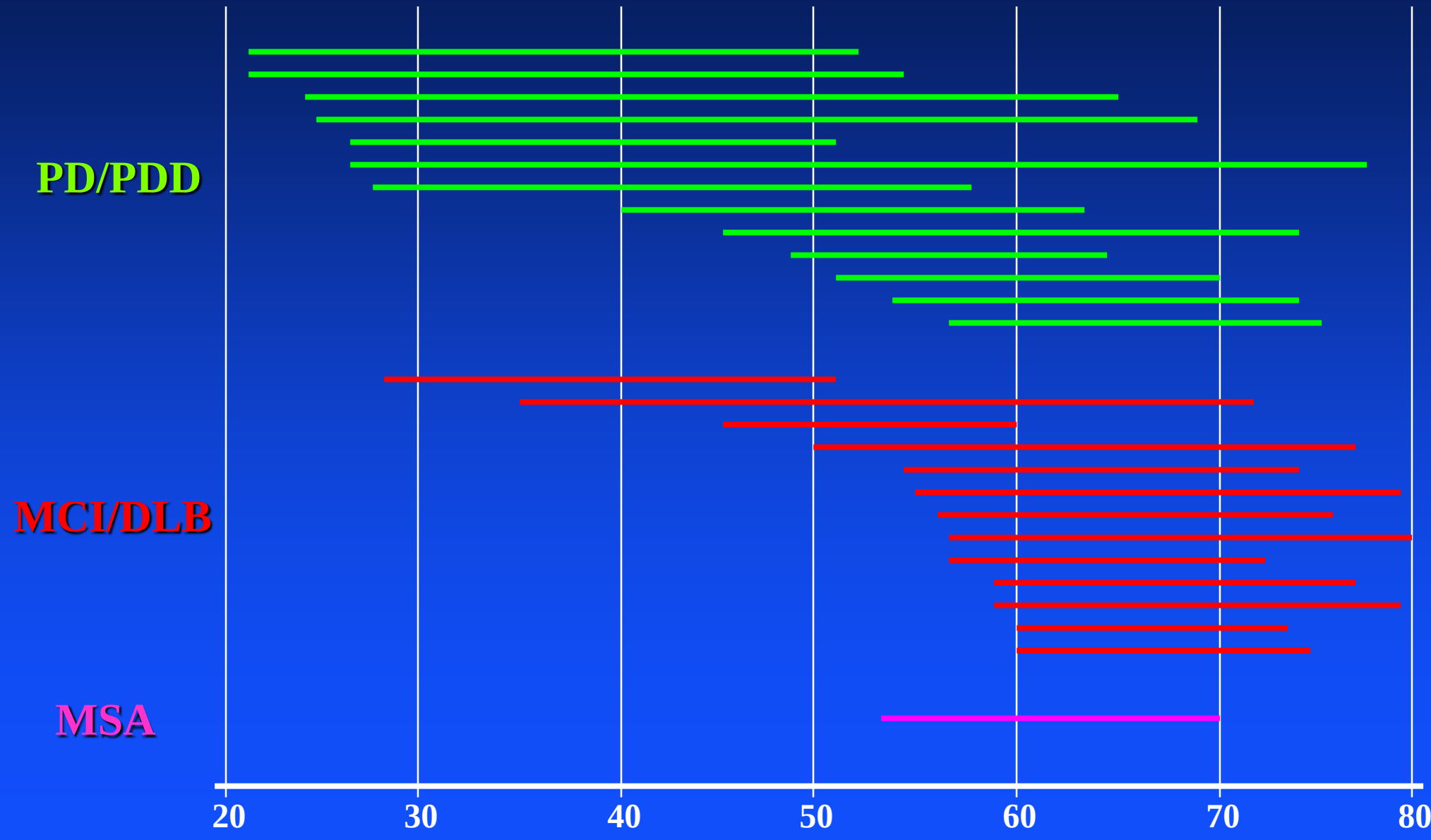
D.O. Claassen, MD
K.A. Josephs, MD, MST
J.E. Ahlskog, MD, PhD
M.H. Silber, MB, ChB
M. Tippmann-Peikert, MD
B.F. Boeve, MD

REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century

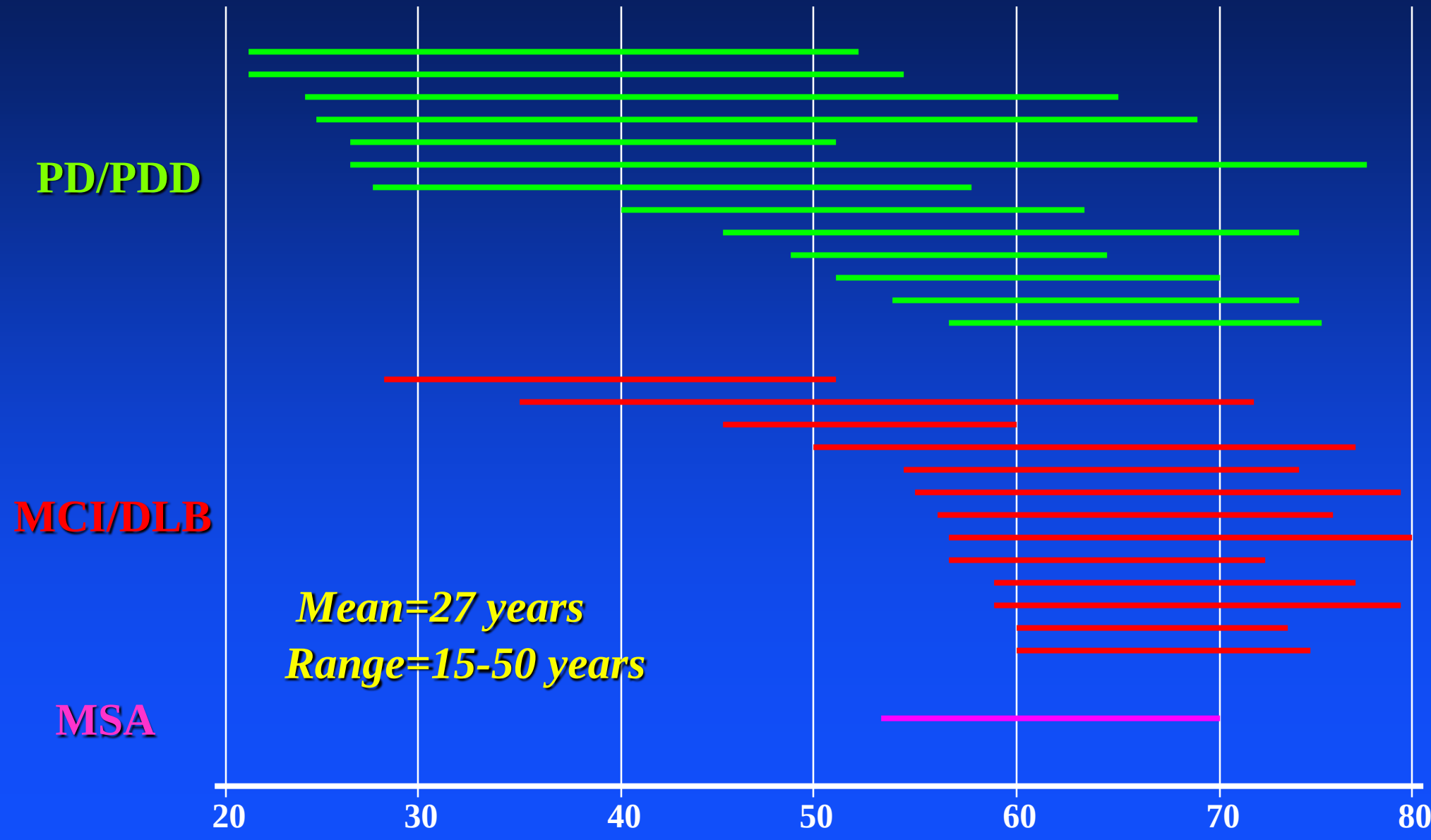


Claassen et al, Neurology 2011

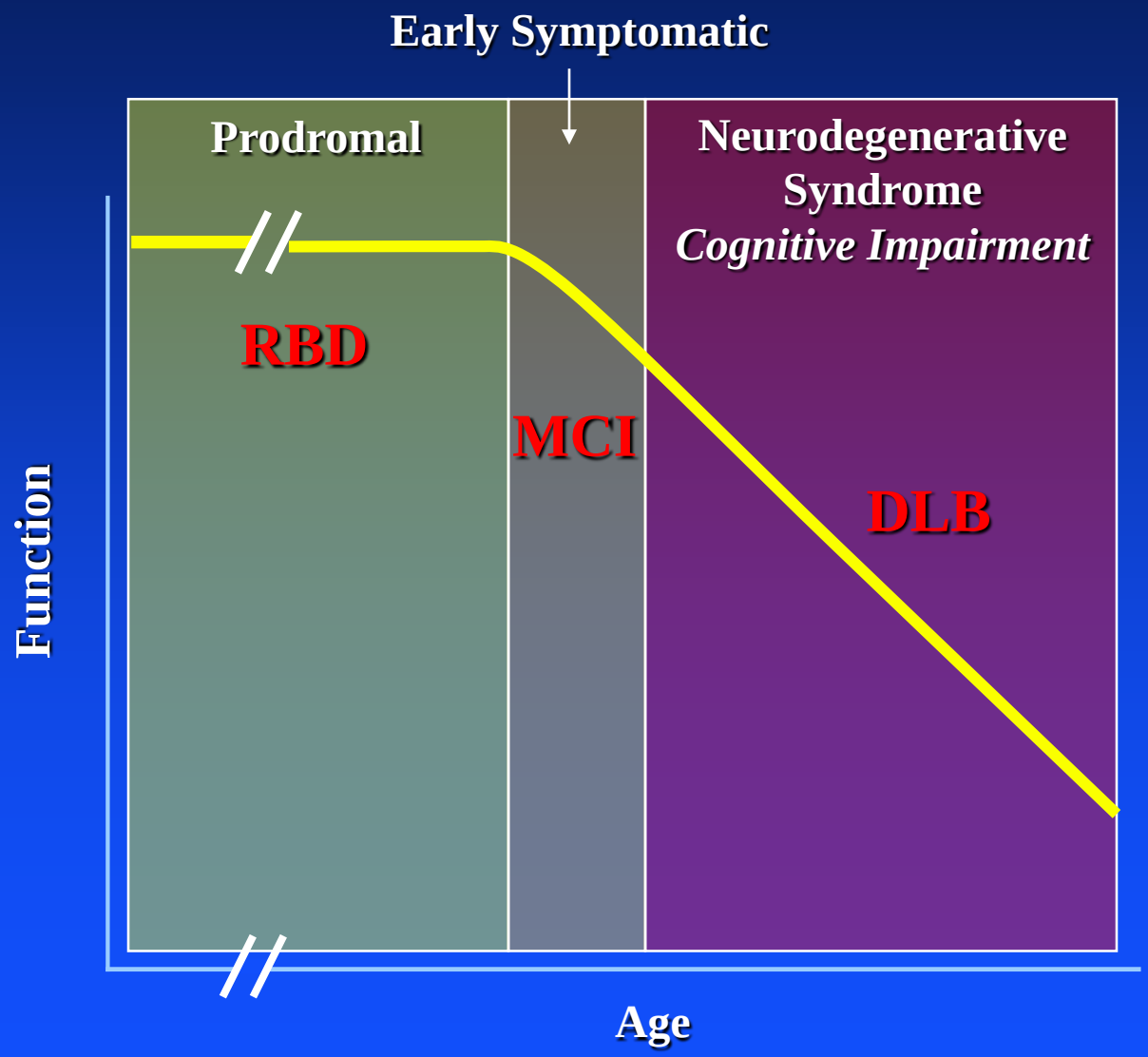
RBD Tends to Precede Cognitive Impairment and/or Parkinsonism by Years or Decades



RBD Tends to Precede Cognitive Impairment and/or Parkinsonism by Years or Decades



RBD and the Association With Lewy Body Disease/Dementia With Lewy Bodies



REM Sleep Behavior Disorder and Relevance To Dementia/Neurodegenerative Disease

Salient Points:

- RBD is often associated with the synucleinopathies, and usually precedes the other "classic" features of DLB, PD or MSA by years

- RBD associated with cognitive impairment/dementia almost always reflects underlying Lewy body disease (ie, DLB)

- Treatment directed toward LBD pathophysiology in those with RBD could delay the onset or prevent the development of DLB

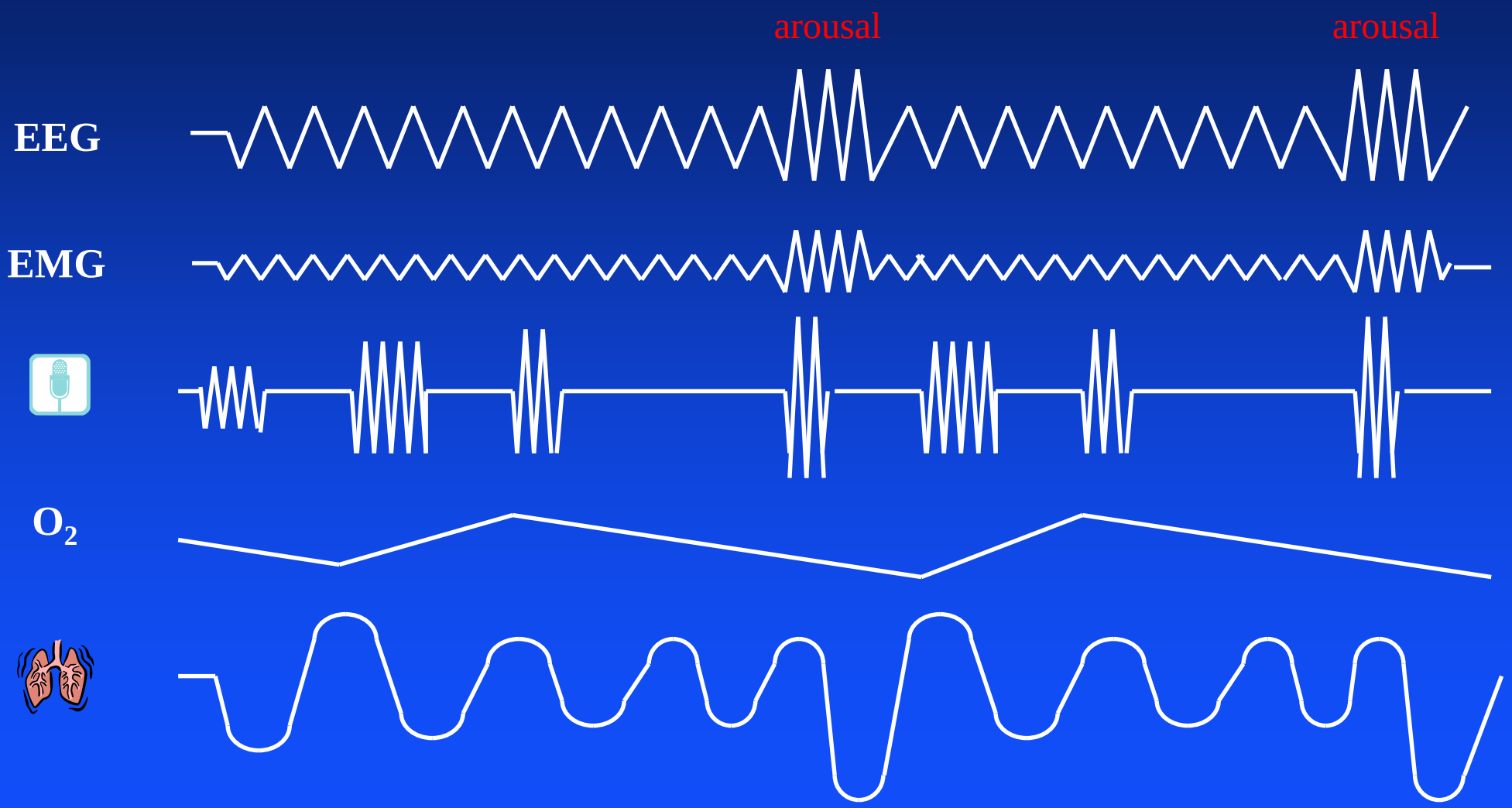
Obstructive Sleep Apnea

Obstructive Sleep Apnea
Clinical Features

- loud and disruptive snoring
- witnessed snorts, gasps, and apnea
- snort arousals
- daytime hypersomnolence
- cognitive impairment
- depression, irritability
- reduced quality of life

Obstructive Sleep Apnea

Polysomnographic Features



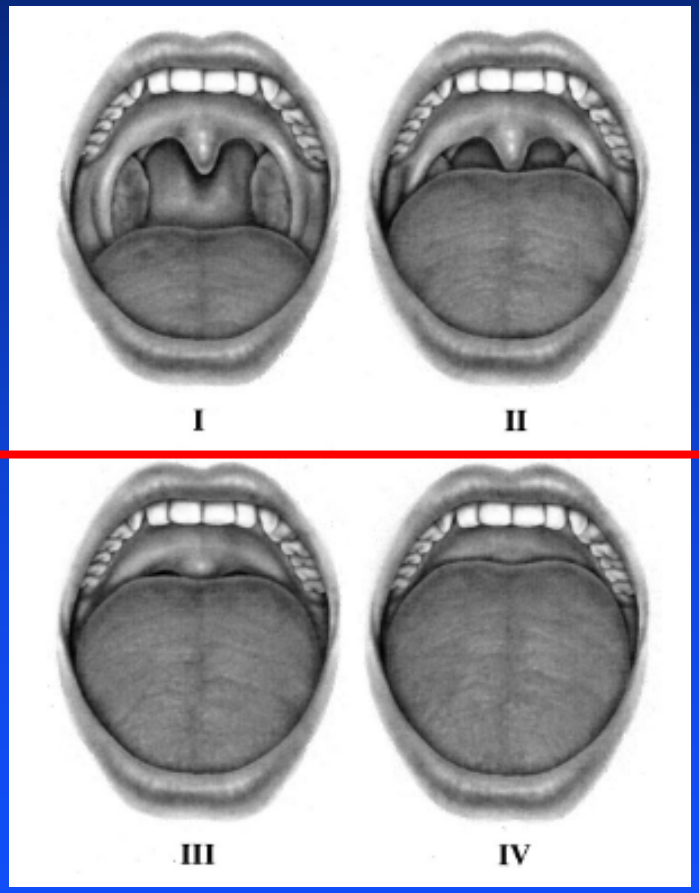
Obstructive Sleep Apnea
Etiology/Pathophysiology

- Repetitive episodes of reduced or ceased airflow due to obstruction in the oropharynx during sleep

- Often associated with:
  - obesity
  - excessive neck tissue (collar size >17 ½)
  - large tonsils
  - retrognathia

Obstructive Sleep Apnea
Office Tasks

Friedman Palate Position



Grade III and IV – associated

with increased frequency of OSA

Friedman et al, Laryngoscope 2004;114:454–459

Obstructive Sleep Apnea
Management

- nasal continuous positive airway pressure (CPAP)
- positional OSA - “tennis balls in a T-shirt” technique
- oral appliance
- uvulopalatopharyngoplasty (UPPP)

Obstructive Sleep Apnea
Nasal CPAP

Obstructive Sleep Apnea

- Untreated OSA in the nondemented population causes cognitive impairment, excessive daytime somnolence (EDS), and diminished mood and quality of life

- Treatment of OSA with nasal continuous positive airway pressure (CPAP) improves cognitive performance, EDS, mood and quality of life

- Neuropsychological analyses have revealed that in patients with OSA, cognitive flexibility, attention, processing speed, and memory all improve with CPAP therapy

Obstructive Sleep Apnea

OSA should be considered one of the reversible causes of cognitive impairment/delirium/dementia

Obstructive Sleep Apnea
Relevance to MCI/AD

Cognitive Effects of Treating Obstructive Sleep Apnea in Alzheimer's Disease: A Randomized Controlled Study

Sonia Ancoli-Israel, PhD,[*†] *Barton W. Palmer, PhD,*[*†] *Jana R. Cooke, MD,*[†‡] *Jody Corey-Bloom, MD, PhD,*[†§] *Lavinia Fiorentino, PhD,*[‖] *Loki Natarajan, PhD,*[#] *Lianqi Liu, MD,*[*†] *Liat Ayalon, PhD,*[*] *Feng He, MS,*[#] *and Jose S. Loredo, MD*[†‡]

JAGS 2008

Sustained Use of CPAP Slows Deterioration of Cognition, Sleep, and Mood in Patients with Alzheimer's Disease and Obstructive Sleep Apnea: A Preliminary Study

Jana R. Cooke, M.D.[1,5]; Liat Ayalon, Ph.D.[2]; Barton W. Palmer, Ph.D.[2]; Jose S. Loredo, M.D.[1,5]; Jody Corey-Bloom, M.D., Ph.D.[4,5]; Loki Natarajan, Ph.D.[3]; Lianqi Liu, M.D.[2]; Sonia Ancoli-Israel, Ph.D.[2]

JCSM 2009

Obstructive Sleep Apnea
Relevance to MCI/AD

Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women

Kristine Yaffe, MD
Alison M. Laffan, PhD
Stephanie Litwack Harrison, MPH
Susan Redline, MD, MPH
Adam P. Spira, PhD
Kristine E. Ensrud, MD
Sonia Ancoli-Israel, PhD
Katie L. Stone, PhD

Conclusion Among older women, those with sleep-disordered breathing compared with those without sleep-disordered breathing had an increased risk of developing cognitive impairment.

JAMA. 2011;306(6):613-619 www.jama.com

Adjusted odds ratio of 1.85

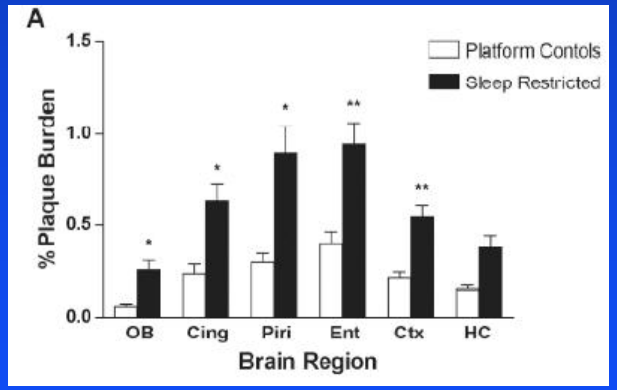
JAMA 2011

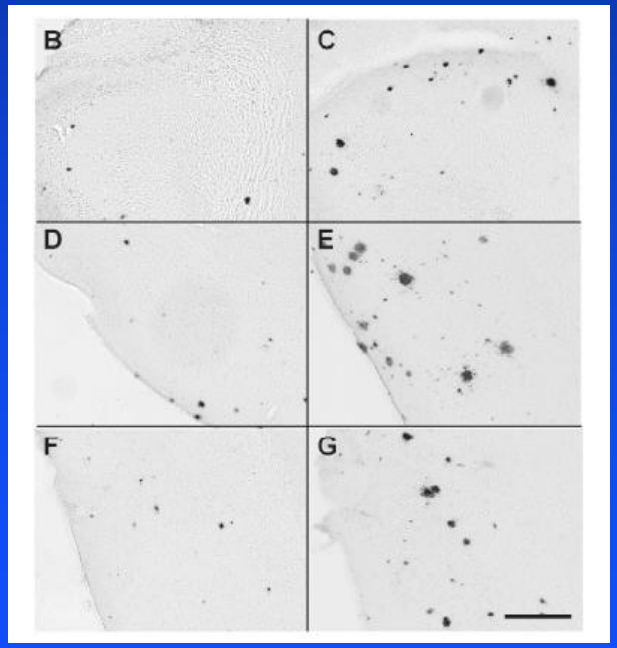
Obstructive Sleep Apnea
Relevance to MCI/AD

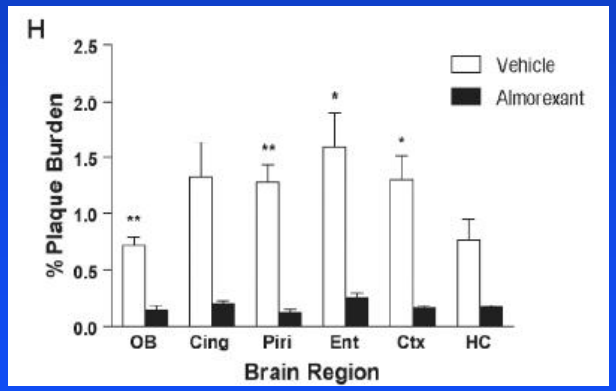
Sciencexpress Report

Amyloid-β Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle

Jae-Eun Kang,[1] Miranda M. Lim,[1] Randall J. Bateman,[1,2,3] James J. Lee,[1] Liam P. Smyth,[1] John R. Cirrito,[1,2] Nobuhiro Fujiki,[4] Seiji Nishino,[4] David M. Holtzman[1,2,3,5*]







Kang et al., Science Express 2009

Obstructive Sleep Apnea
Relevance to MCI/AD

Sleep and Alzheimer disease pathology —a bidirectional relationship

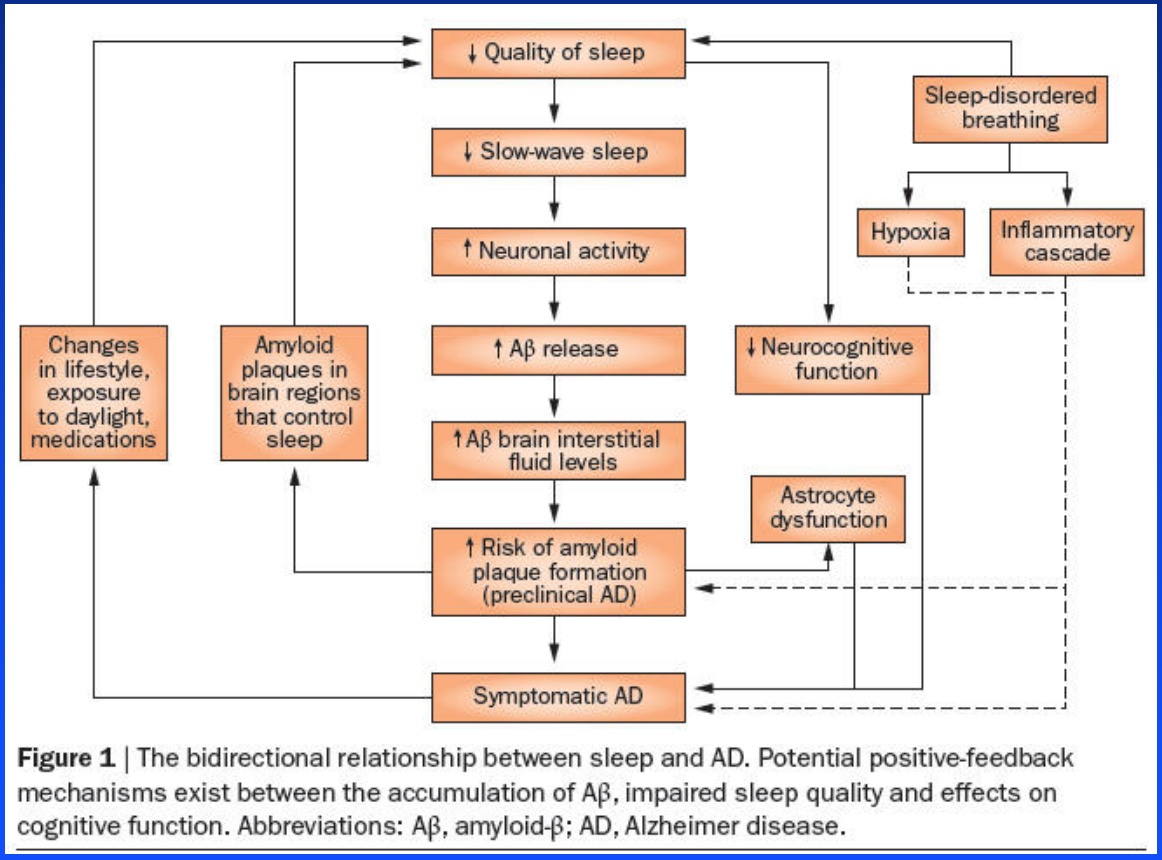


Figure 1 | The bidirectional relationship between sleep and AD. Potential positive-feedback mechanisms exist between the accumulation of Aβ, impaired sleep quality and effects on cognitive function. Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease.

Ju et al., Nature Rev Neurosci 2014

Obstructive Sleep Apnea
Relevance to MCI/AD

Published Ahead of Print on April 15, 2015 as 10.1212/WNL.0000000000001566

Sleep-disordered breathing advances cognitive decline in the elderly

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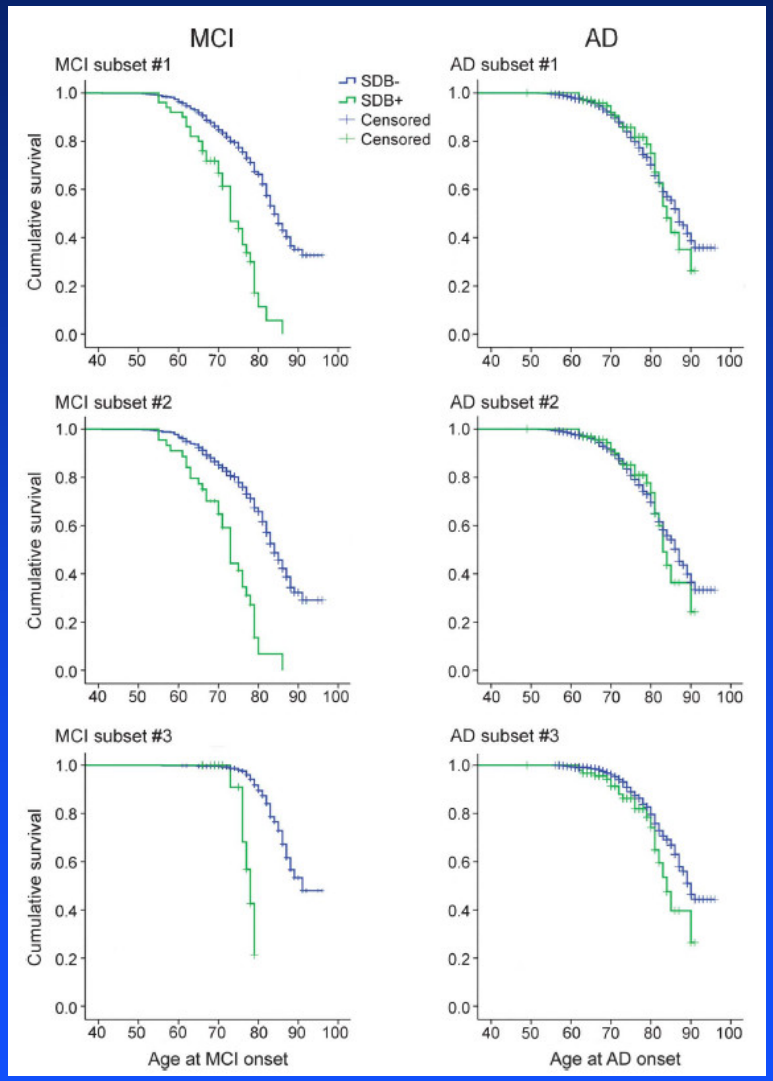
Shou-en Lu, PhD
Jason Lim, BA
Margaret E. Wohlleber, BA
Emma L. Ducca, BA
Viachaslau Koushyk, MD
Lidia Glodzik, MD
Lisa Mosconi, PhD
Indu Ayappa, PhD
David M. Rapoport, MD
Mony J. de Leon, EdD
For the Alzheimer's Disease Neuroimaging Initiative

Osario et al., Neurology 2015

Obstructive Sleep Apnea
Relevance to MCI/AD

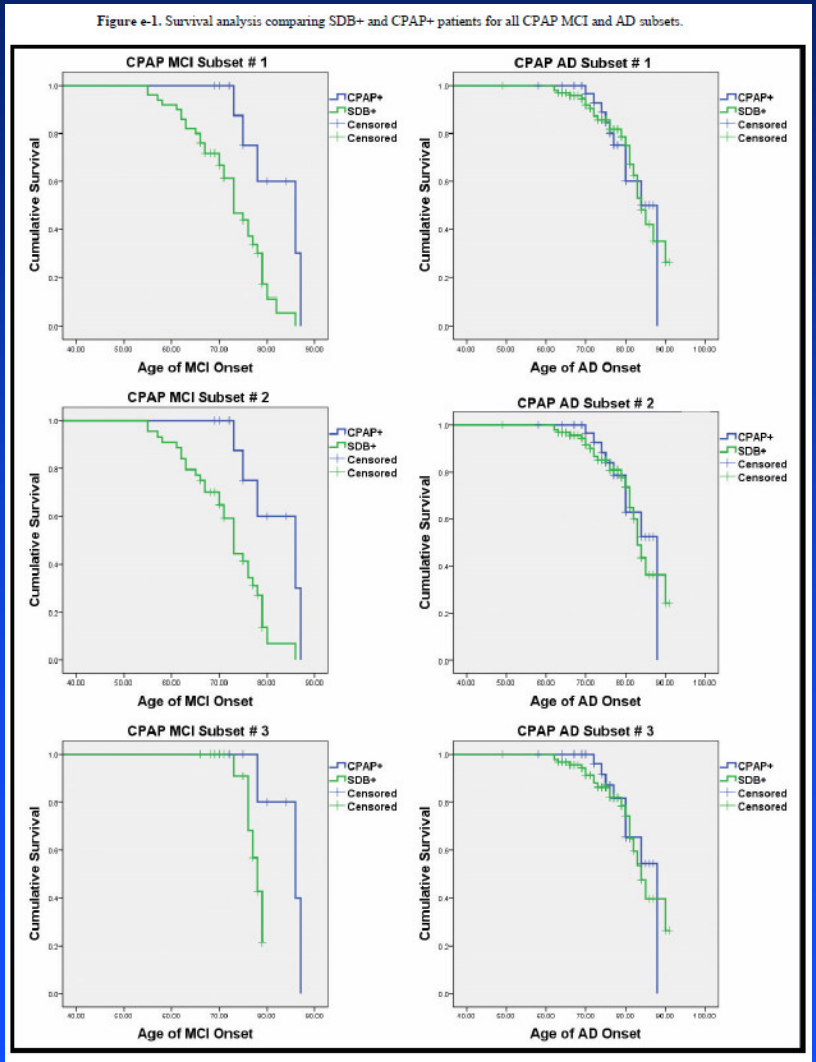


OSA ~ sleep disordered breathing (SDB)

+SDB compared to no SDB was associated with earlier age of onset of MCI (and AD)

Osario et al., Neurology 2015

Obstructive Sleep Apnea
Relevance to MCI/AD



Among those with SDB:

CPAP use associated with delayed age of onset of MCI

Osario et al., Neurology 2015

Obstructive Sleep Apnea and Relevance To Dementia/Neurodegenerative Disease

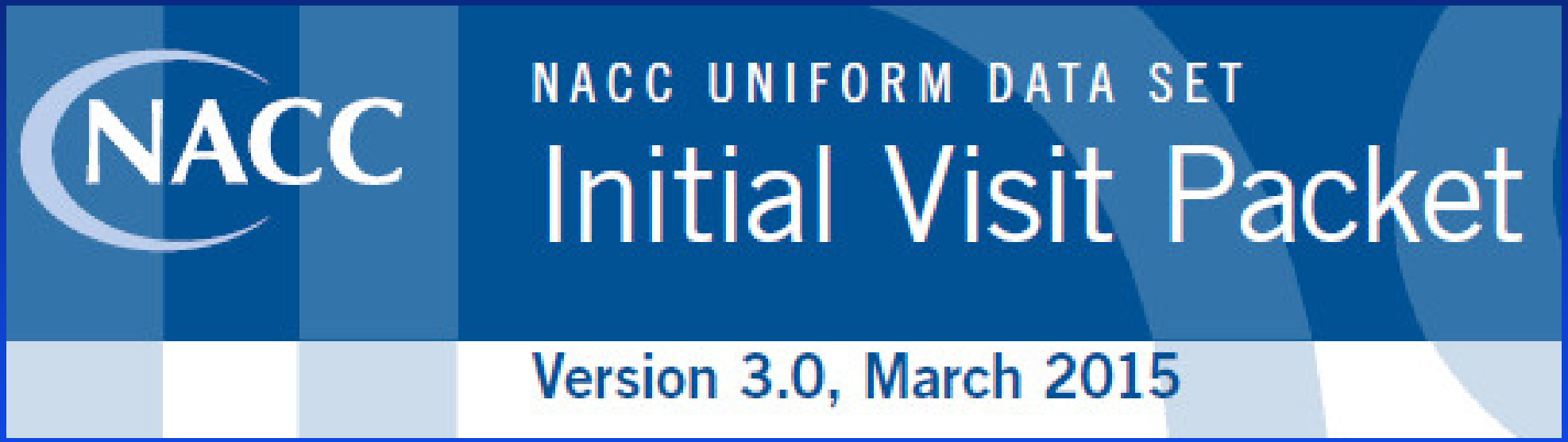
Salient Points:

- OSA is associated with cognitive impairment, MCI and AD

- Evidence suggests:
  - OSA increases risk of MCI/AD
  - OSA decreases age of onset of MCI +/- AD
  - CPAP improves cognition in those with MCI/AD
  - CPAP delays development of MCI +/- AD

  - OSA may alter intracranial amyloid physiology

Sleep-Related Topics of Interest in the ADC Program/NACC



Sleep-Related Topics of Interest in the ADC Program/NACC

NACC UNIFORM DATA SET
Initial Visit Packet
Version 3.0, March 2015

INITIAL VISIT PACKET NACC UNIFORM DATA SET (UDS)

Form A5: Subject Health History

5. Medical conditions (cont.)	Absent	Recent/ active	Remote/ inactive	Unknown
5g. Incontinence — urinary	☐ 0	☐ 1	☐ 2	☐ 9
5h. Incontinence — bowel	☐ 0	☐ 1	☐ 2	☐ 9
5i. Sleep apnea	☐ 0	☐ 1	☐ 2	☐ 9
5j. REM sleep behavior disorder (RBD)	☐ 0	☐ 1	☐ 2	☐ 9
5k. Hyposomnia/insomnia	☐ 0	☐ 1	☐ 2	☐ 9
5l. Other sleep disorder (SPECIFY): _____	☐ 0	☐ 1	☐ 2	☐ 9

Sleep-Related Topics of Interest in the ADC Program/NACC

NACC UNIFORM DATA SET
Initial Visit Packet
Version 3.0, March 2015

INITIAL VISIT PACKET NACC UNIFORM DATA SET (UDS)

Form B9: Clinician Judgment of Symptoms

	No	Yes	Unknown
9g. **Personality change** Does the subject exhibit bizarre behavior or behavior uncharacteristic of the subject, such as unusual collecting, suspiciousness (without delusions), unusual dress, or dietary changes? Does the subject fail to take others' feelings into account?	☐ 0	☐ 1	☐ 9
9h. **REM sleep behavior disorder** While sleeping, does the subject appear to act out his/her dreams (e.g., punch or flail their arms, shout, or scream)?	☐ 0	☐ 1	☐ 9
9h1. If yes, at what age did the REM sleep behavior disorder begin? ___ ___ ___ (The clinician must use his/her best judgment to estimate an age of onset.)			
9i. **Anxiety** For example, does s/he show signs of nervousness (e.g., frequent sighing, anxious facial expressions, or hand-wringing) and/or excessive worrying?	☐ 0	☐ 1	☐ 9

Sleep-Related Topics of Interest in the ADC Program/NACC

NACC UNIFORM DATA SET
Initial Visit Packet
Version 3.0, March 2015

INITIAL VISIT PACKET NACC UNIFORM DATA SET (UDS)

Form B9: Clinician Judgment of Symptoms

21. Indicate the **predominant** domain that was first recognized as changed in the subject:	☐ 1 Cognition ☐ 2 Behavior ☐ 3 Motor function ☐ 8 N/A ☐ 9 Unknown

Reminder: RBD is recorded under the "behavior" domain, and when present, usually precedes changes in cognition and motor functioning – this box should be checked in such instances

Sleep-Related Topics of Interest in the ADC Program/NACC

NACC UNIFORM DATA SET
Initial Visit Packet
Version 3.0, March 2015

INITIAL VISIT PACKET NACC UNIFORM DATA SET (UDS)

Form D2: Clinician-assessed Medical Conditions

14. Sleep apnea	☐ 0	☐ 1	☐ 8
15. REM sleep behavior disorder (RBD)	☐ 0	☐ 1	☐ 8
16. Hyposomnia/insomnia	☐ 0	☐ 1	☐ 8
17. Other sleep disorder (SPECIFY): _____	☐ 0	☐ 1	☐ 8

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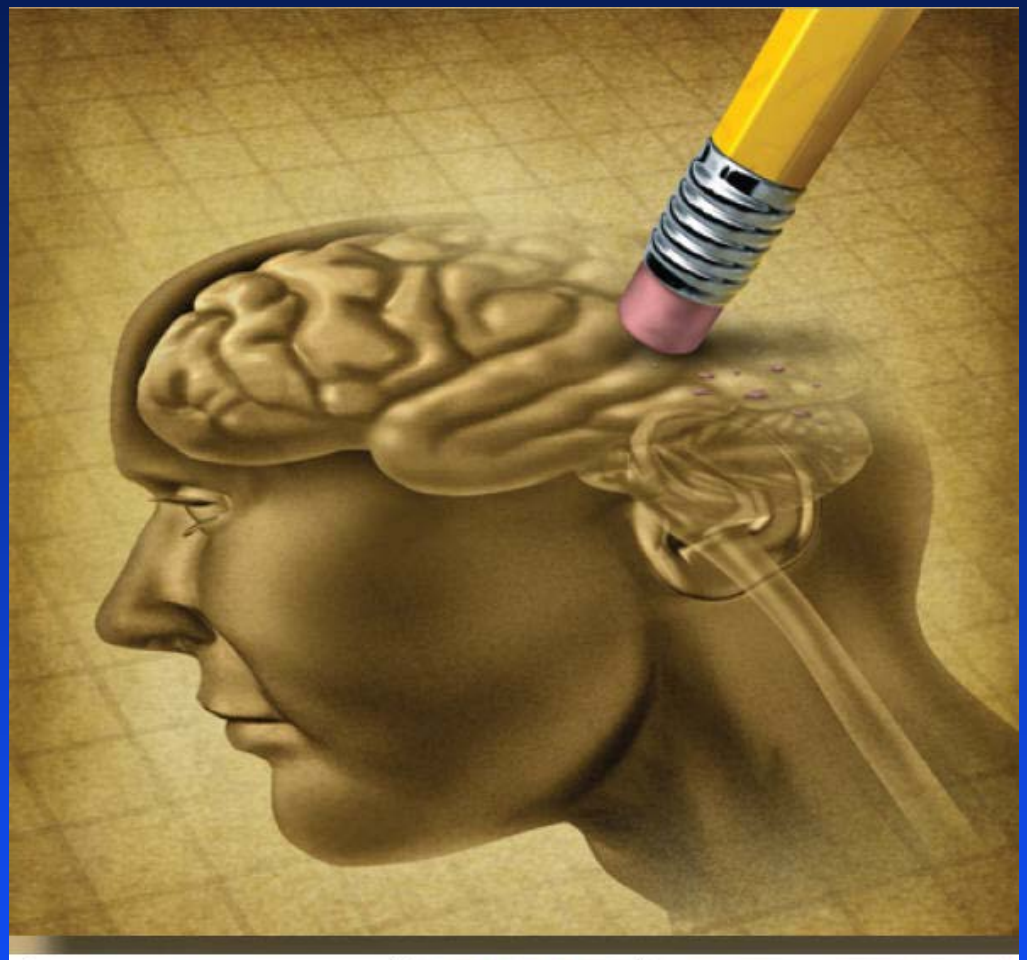
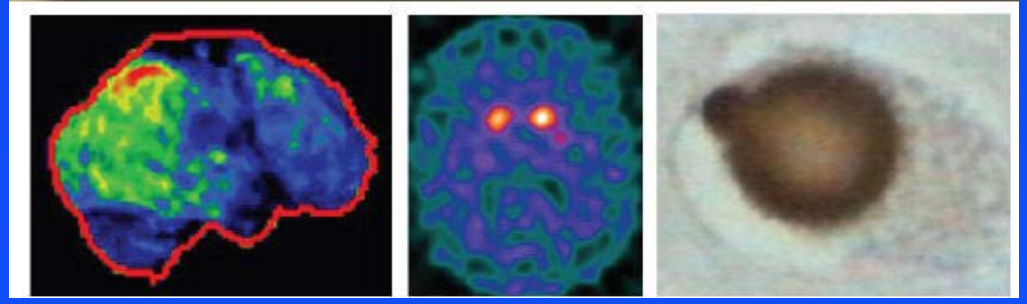
Supported by grants AG015866, AG006786, AG016574 from the NIA, the Alzheimer's Association, and the Mangurian Foundation

International Dementia with Lewy Bodies Conference





December 1-4, 2015

Marriott Harbor Beach Resort & Spa

Fort Lauderdale, Florida

Abstract Deadline – June 2015

Diagnosis
Epidemiology
Clinical aspects
Neuropsychology
Neuroimaging
Therapeutics

Genetics
Biofluid markers
Neuropathology
Molecular biology
Animal models
Controversies

RBD – Lewy Body Disease Association

Mild cognitive impairment associated with limbic and neocortical lewy body disease: a clinicopathological study

Jennifer Molano,[1] Bradley Boeve,[1] Tanis Ferman,[2] Glenn Smith,[2] Joseph Parisi,[1,3] Dennis Dickson,[4] David Knopman,[1] Neill Graff-Radford,[1] Yonas Geda,[2] John Lucas,[2] Kejal Kantarci,[5] Maria Shiung,[5] Clifford Jack,[5] Michael Silber,[1] V. Shane Pankratz[6] and Ronald Petersen[1,6]

Table 1 Clinical features of eight patients with mild cognitive impairment ± subsequent dementia associated with Lewy body disease pathology

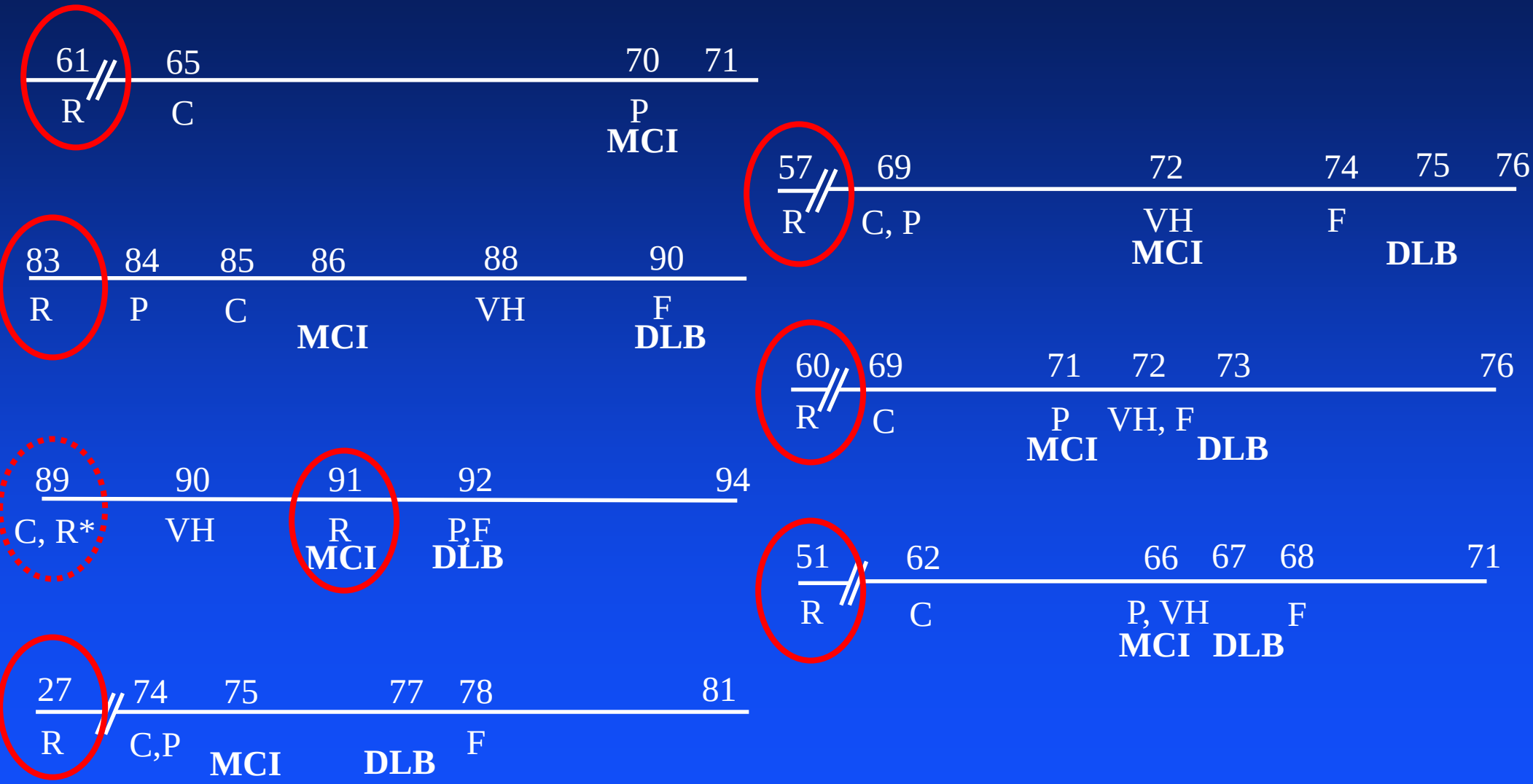
Case	Sex	Educational level in years	Age of RBD onset in years	Age of cognitive symptom onset in years	Age of MCI diagnosis in years	Age of parkinsonism onset in years	Age of VH onset in years	Fluctuations based on MFS, and onset in years	MCI subtype and specific cognitive domains of impairment	Age at conversion from MCI to dementia in years	Age of death in years
1	M	16	61	66	70	71	–	No	md-MCI-na Attention/visuospatial	–	71
2	M	10	83	85	86	84	88	Yes 90	sd-MCI-na Attention	88	90
3	M	14	57 PSG+	69	70	69	72	Yes 74	sd-MCI-na Attention	75	76
4	F	13	91 PSG+	89	91	92	90	Yes 92	md-MCI-na Attention/visuospatial	92	94
5	M	16	27 PSG+	74	75	74	–	Yes 78	md-MCI-na Attention/visuospatial	77	81
6	M	12	51	62	66	66	66	Yes 68	md-MCI+a Memory/attention/visuospatial	67	71
7	M	14	60 PSG+	69	71	71	72	Yes 72	md-MCI+a Memory/language/visuospatial	73	76
8	F	12	–	67	67	69	64	No (no MFS)	md-MCI+a Memory/language/visuospatial	69	73

M = male; F = female; RBD = REM sleep behaviour disorder; PSG + = polysomnogram-proven RBD; MCI = mild cognitive impairment (a = amnestic; na = nonamnestic; sd = single domain; md = multiple domain); VH = visual hallucinations; MFS = Mayo Fluctuations Scale.

Molano et al, Brain 2010

RBD-LBD Association

RBD Precedes Cognitive Impairment/Parkinsonism



Molano et al, Brain 2010

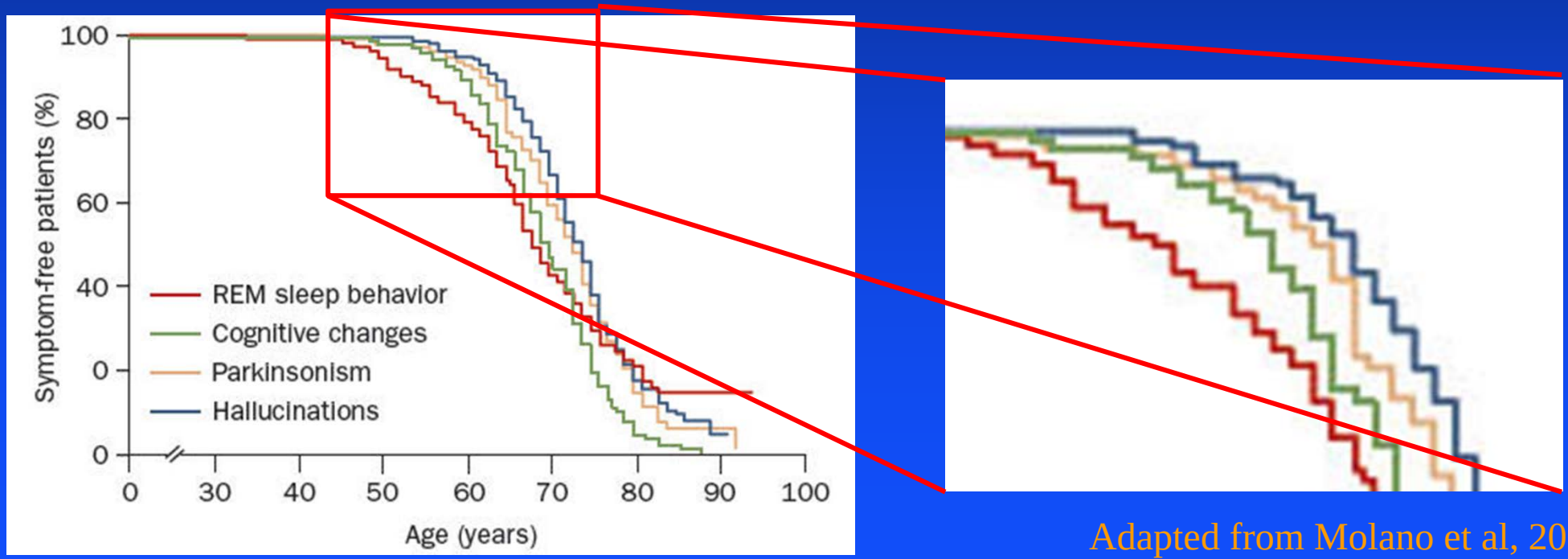
RBD-LBD Association

RBD Precedes Cognitive Impairment/Parkinsonism

General Timeline of Features

Age →

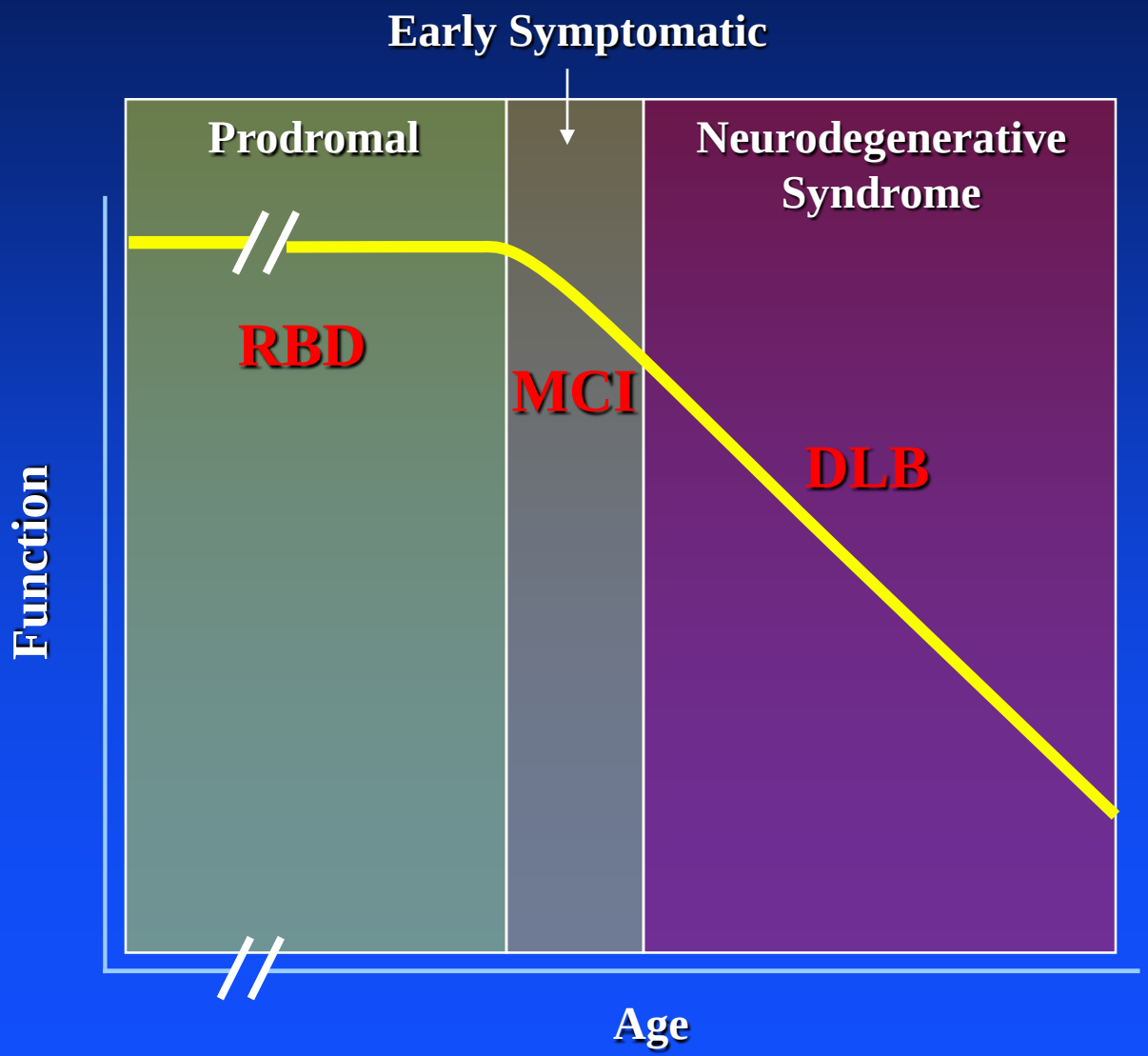
R C P VH F Death



Adapted from Molano et al, 2010 and Fields et al, 2011

RBD-LBD Association

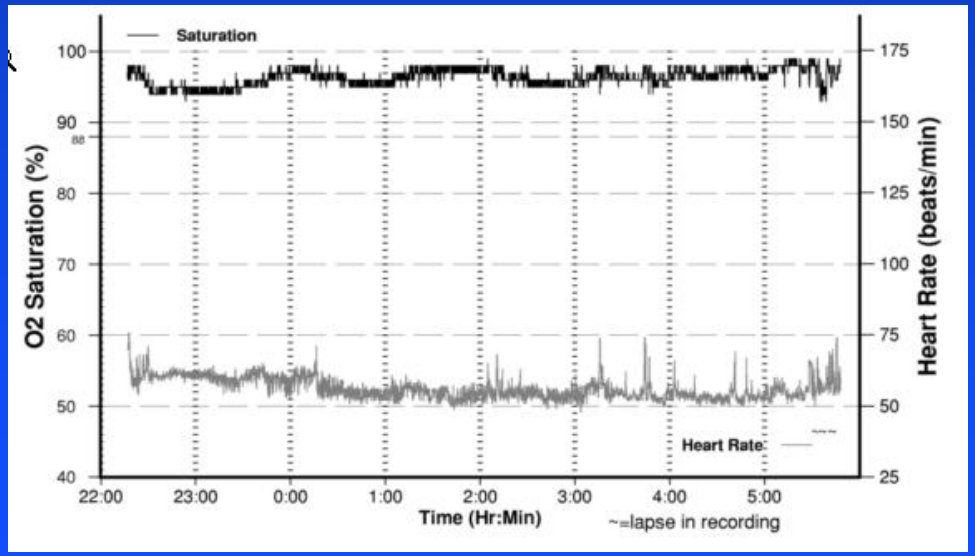
RBD Precedes Cognitive Impairment/Parkinsonism



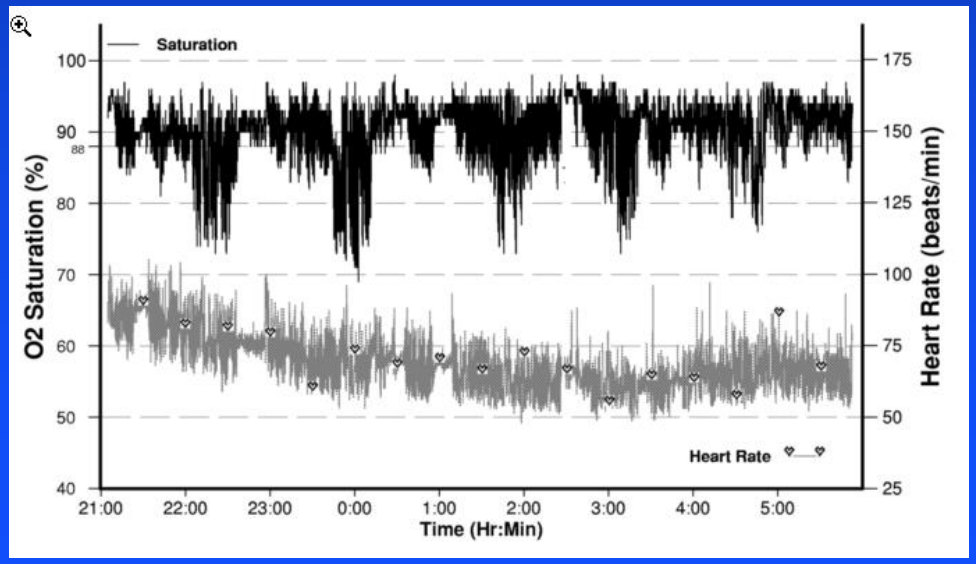
Obstructive Sleep Apnea

Consider screening for OSA with overnight oximetry in appropriate patients

Normal



OSA

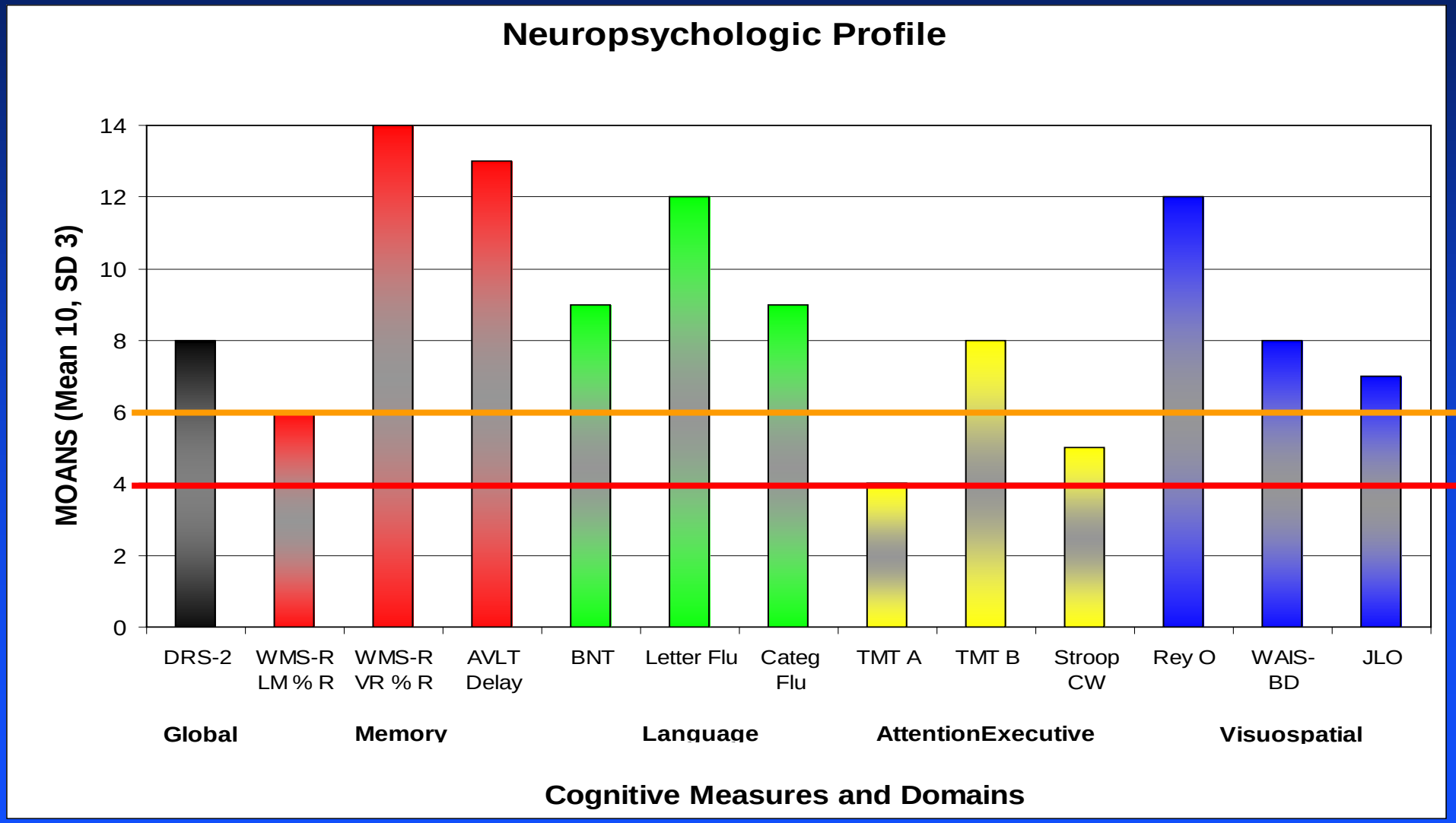


Obstructive Sleep Apnea
Case Example

- 67 yr old woman with 2 year history of cognitive decline
- Forgetful, errors in arranging family activities, multi-tasking difficult
- Rare errors balancing checkbook, but living independently, driving OK

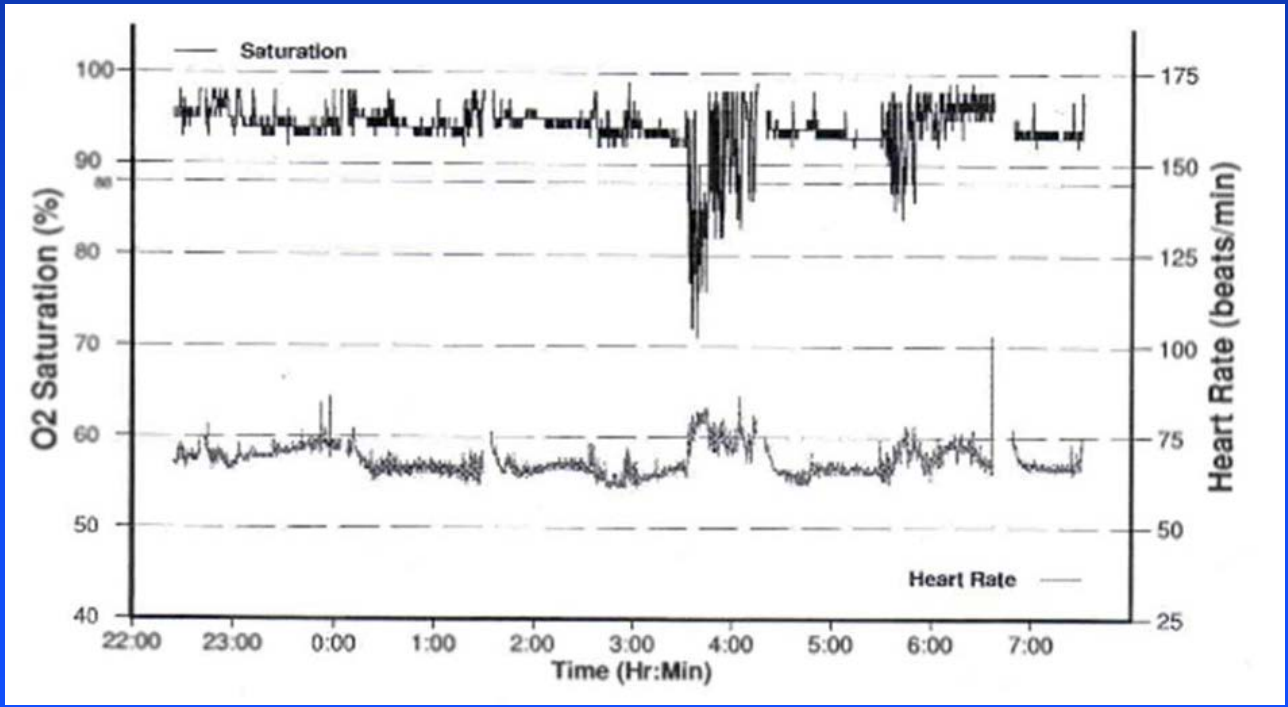
- MMSE 27/30
- General neurologic exam normal
- Crowded oropharynx

Obstructive Sleep Apnea
Case Example



Obstructive Sleep Apnea
Case Example

- Labs normal, MRI head normal
- Dx: mild cognitive impairment
- Overnight oximetry:



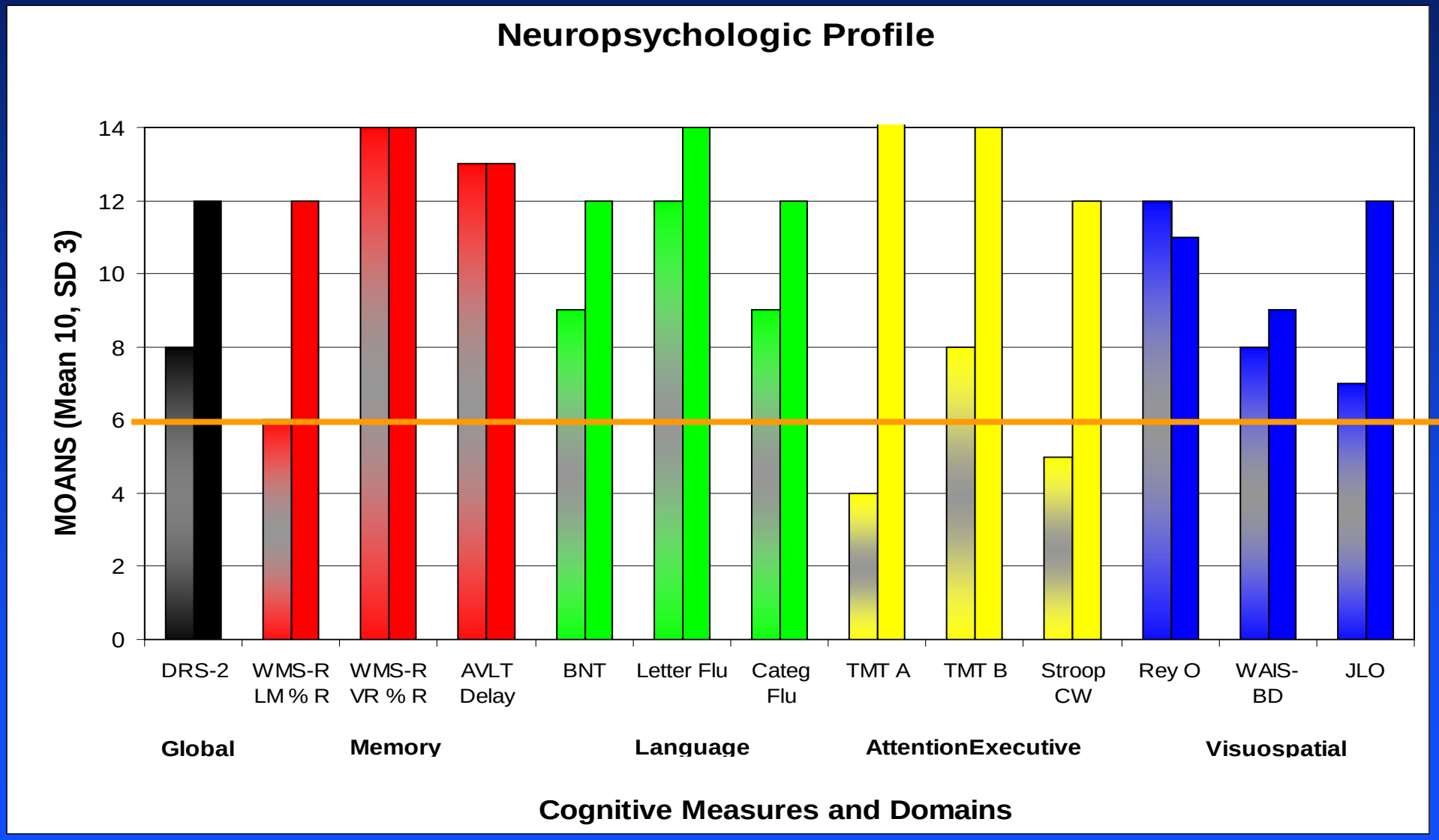
Obstructive Sleep Apnea
Case Example

Case example (cont)

- PSG – moderately severe OSA (AHI >30)
- Commenced on nasal CPAP
- Excellent response, tolerated CPAP well
- Within 1-2 months cognitive problems resolved

- Returned 1 year later

Obstructive Sleep Apnea
Case Example



Dementia with Lewy Bodies
Many Sleep Issues in DLB

Polysomnographic Findings in Dementia With Lewy Bodies

Winnie C. Pao, MD,† Bradley F. Boeve, MD,*† Tanis J. Ferman, PhD,‡ Sioung-Chi Lin, MD,† Glenn E. Smith, PhD,‡ David S. Knopman, MD,* Neill R. Graff-Radford, MBChB,* Ronald C. Petersen, PhD, MD,* Joseph E. Parisi, MD,*§ Dennis W. Dickson, MD,‖ and Michael H. Silber, MBChB*†*

Pao et al, The Neurologist 2013

Dementia with Lewy Bodies
Many Sleep Issues in DLB

TABLE 1. Characteristics and PSG Analysis of 78 Clinically Diagnosed DLB Patients With Sleep-related Complaints

	Mean	SD
Age (y)	71.7	7.7
GLDS (n = 71)	3.7	0.9
DRS (n = 57)	115	18
BMI (n = 48)	26.7	4.6
	n	%
VH	37	47
Parkinsonism	50	64
RBD	65	83
RSWA	66	85
RDI ≥ 5	47	60
RDI ≥ 10	28	36
PLMAI ≥ 5	35	45
AFNARI ≥ 5	59	76
TAI ≥ 5	78	100
SE < 80%	56	72
SE < 70%	38	49
SE < 60%	19	24
	Mean	SD
RDI	11.9	15.8
PLMAI	5.9	8.5
AFNARI	10.7	12
TAI	26.6	17.4

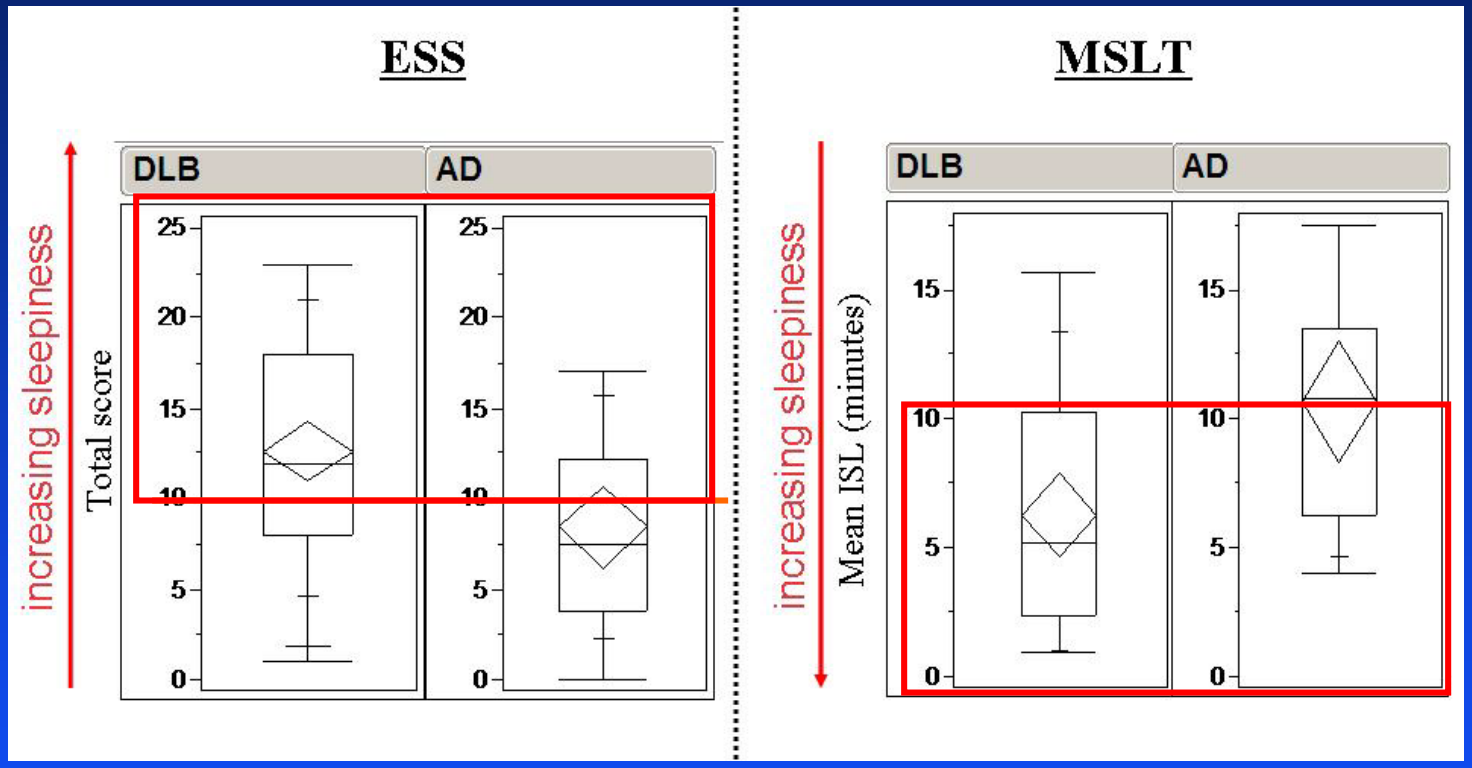
Main points

- RBD is common (83%)
- PLM arousals are common
  - 45% had >5 arousals/hr
- AFNARs are very common
  - 76% had >5 arousals/hr
- Sleep efficiency is poor
  - 72% had <80%
  - 49% had <70%

Pao et al, The Neurologist 2013

Dementia with Lewy Bodies
DLB Patients Are Hypersomnolent

DLB: 57
AD: 27

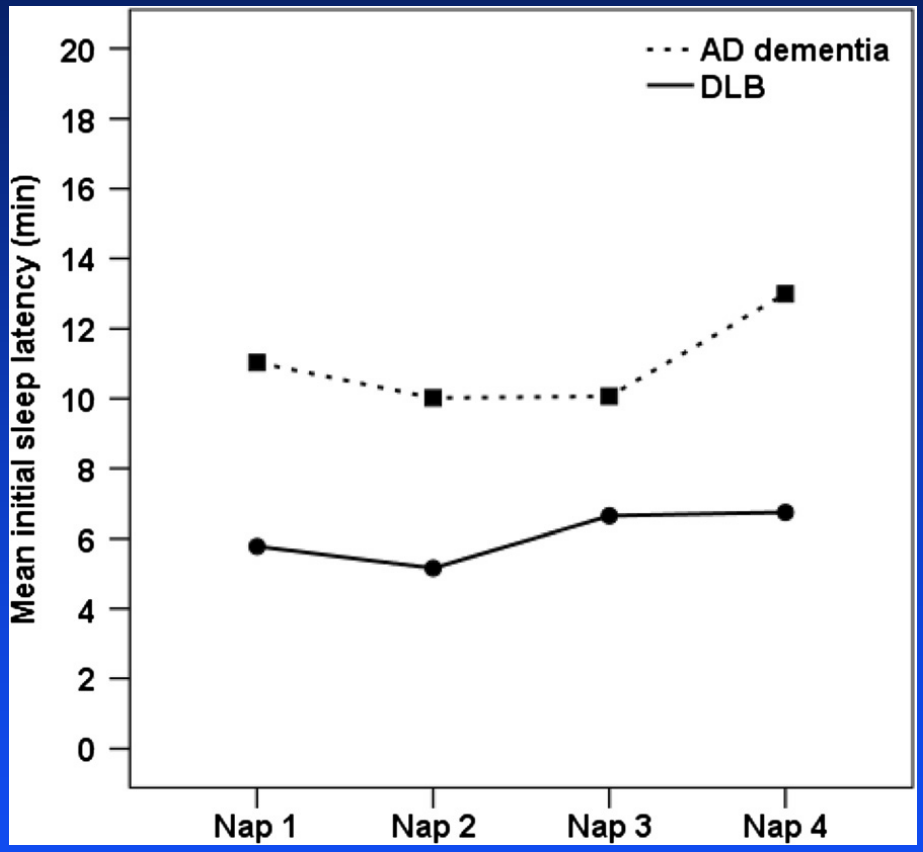


DLB: 31
AD: 14

The data confirms subjective (ESS) and objective evidence of EDS (MSLT) is present in DLB and not in AD.

Ferman et al, Alz Res Therapy 2014

Dementia with Lewy Bodies
DLB Patients Are Hypersomnolent

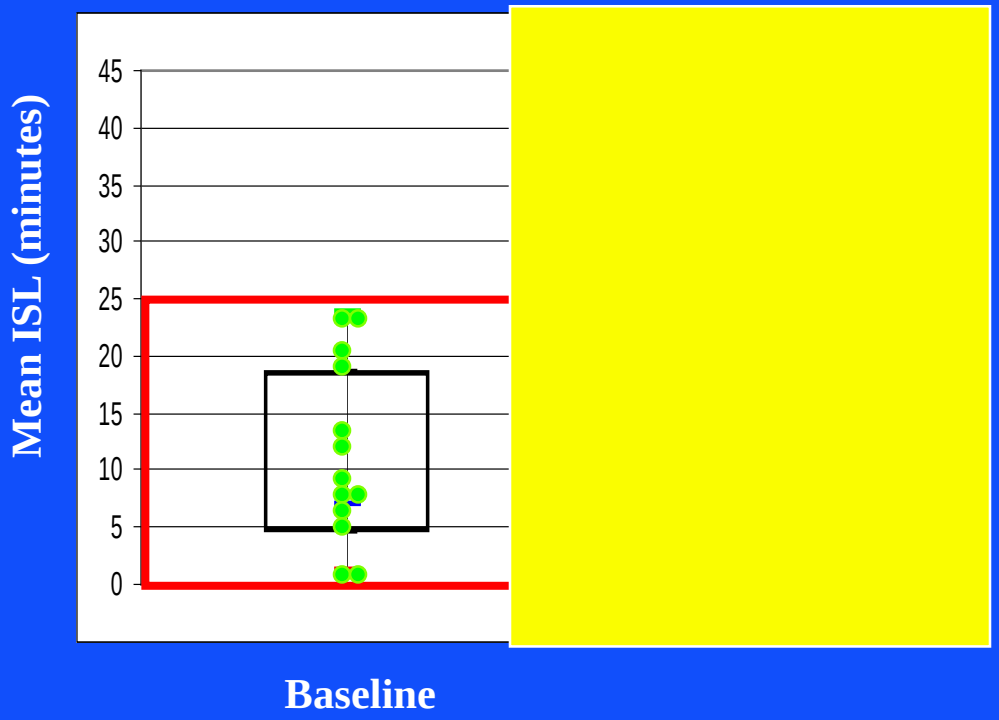


The data suggests that hypersomnia is present in DLB and not in AD.

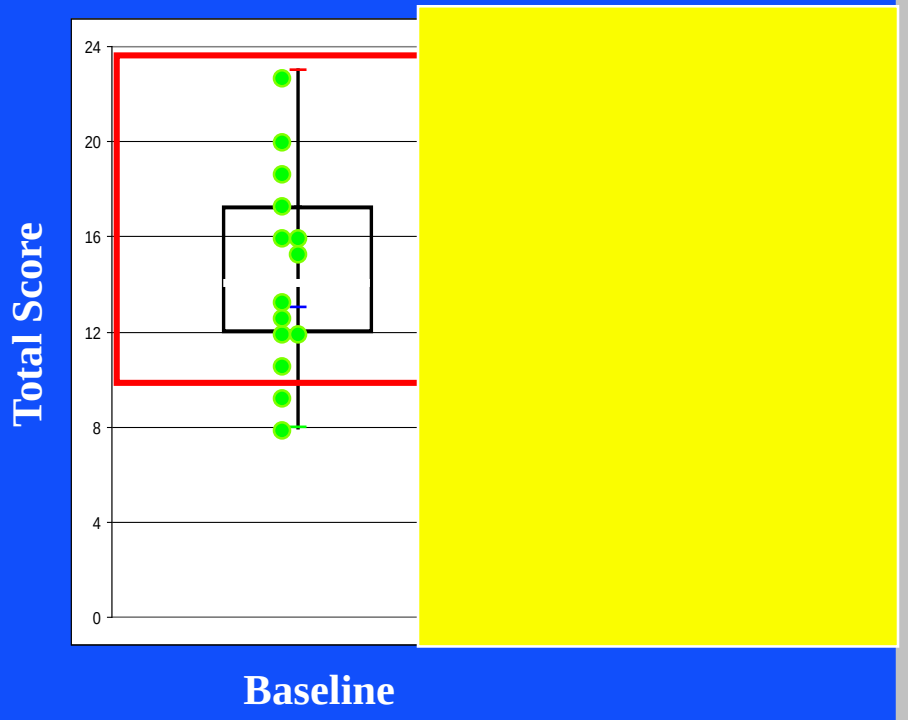
Ferman et al, Alz Res Therapy 2014

Dementia with Lewy Bodies
DLB Patients Struggle to Maintain Wakefulness

Maintenance of Wakefulness Test Results



Epworth Sleepiness Scale Results

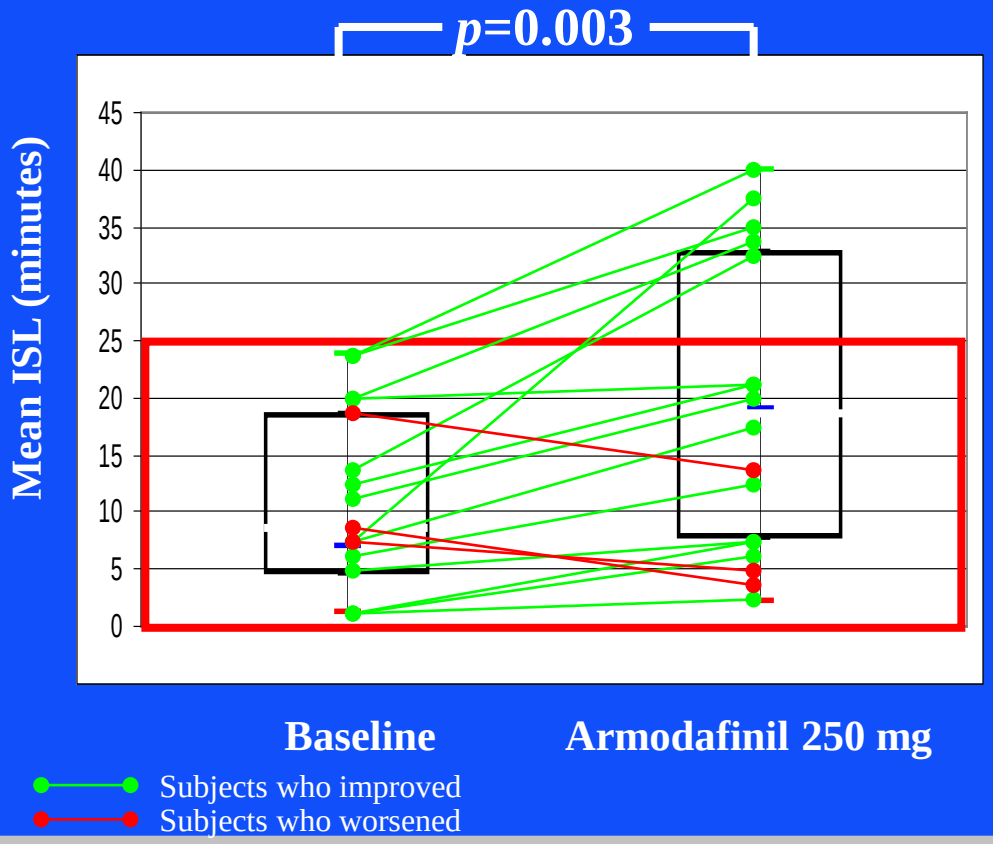


Boeve et al, AAN 2012

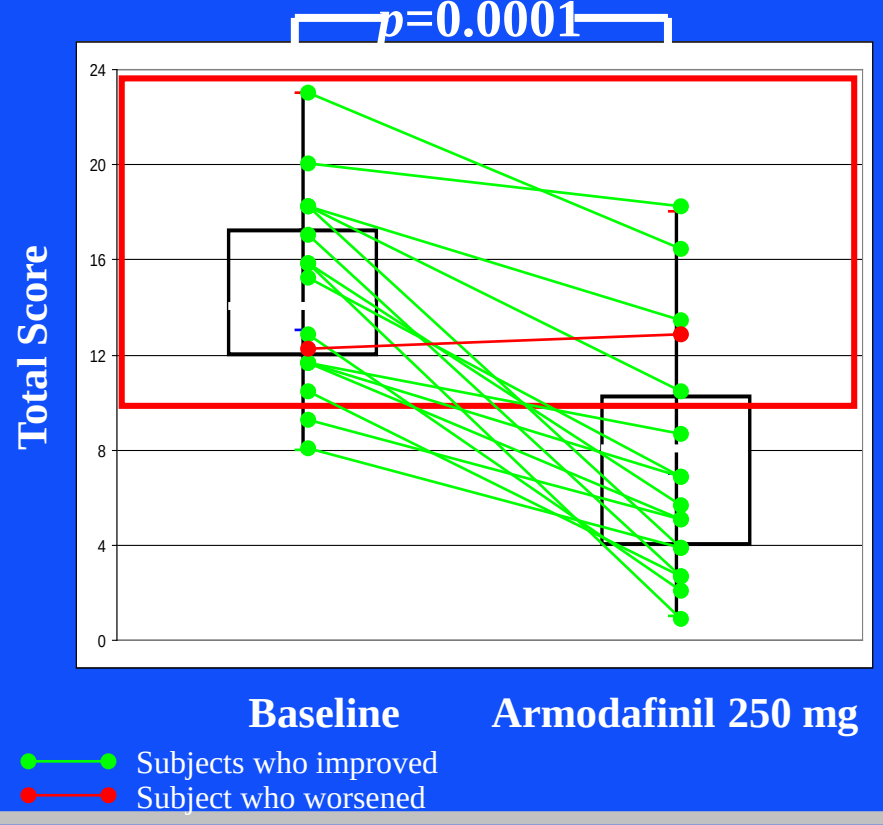
Dementia with Lewy Bodies
DLB Patients Struggle to Maintain Wakefulness

Open label pilot study of armodafinil for treatment of hypersomnia associated with DLB

Maintenance of Wakefulness Test Results



Epworth Sleepiness Scale Results



Boeve et al, AAN 2012

REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Salient Points:

- RBD is common in MCI/DLB and usually precedes the cognitive features by years or decades

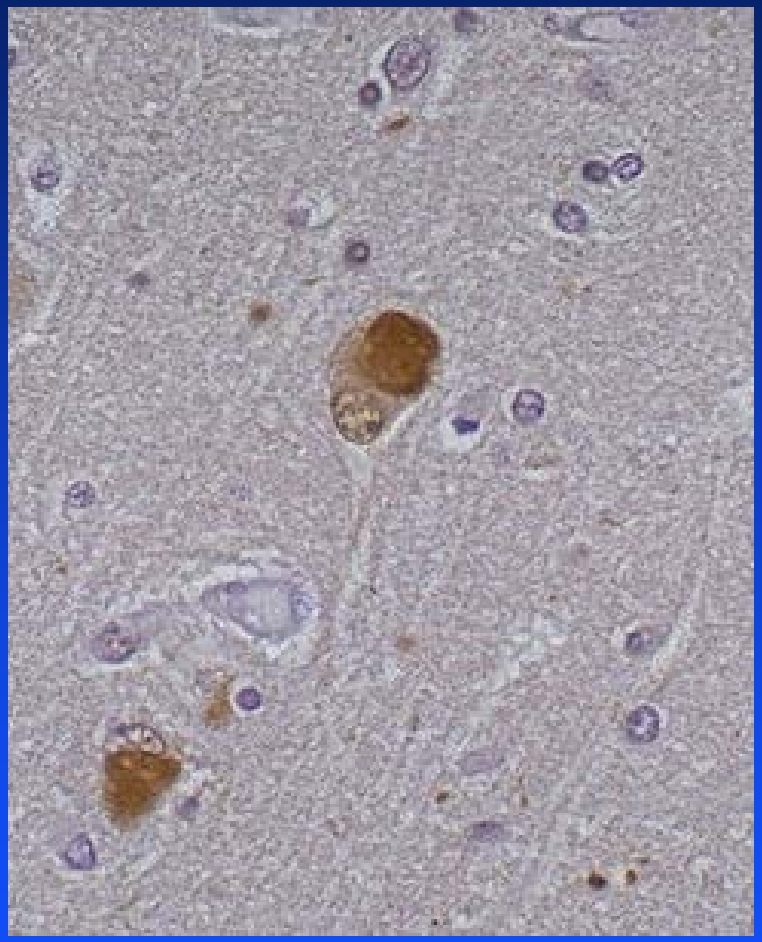
- Many other sleep issues in DLB, including hypersomnia

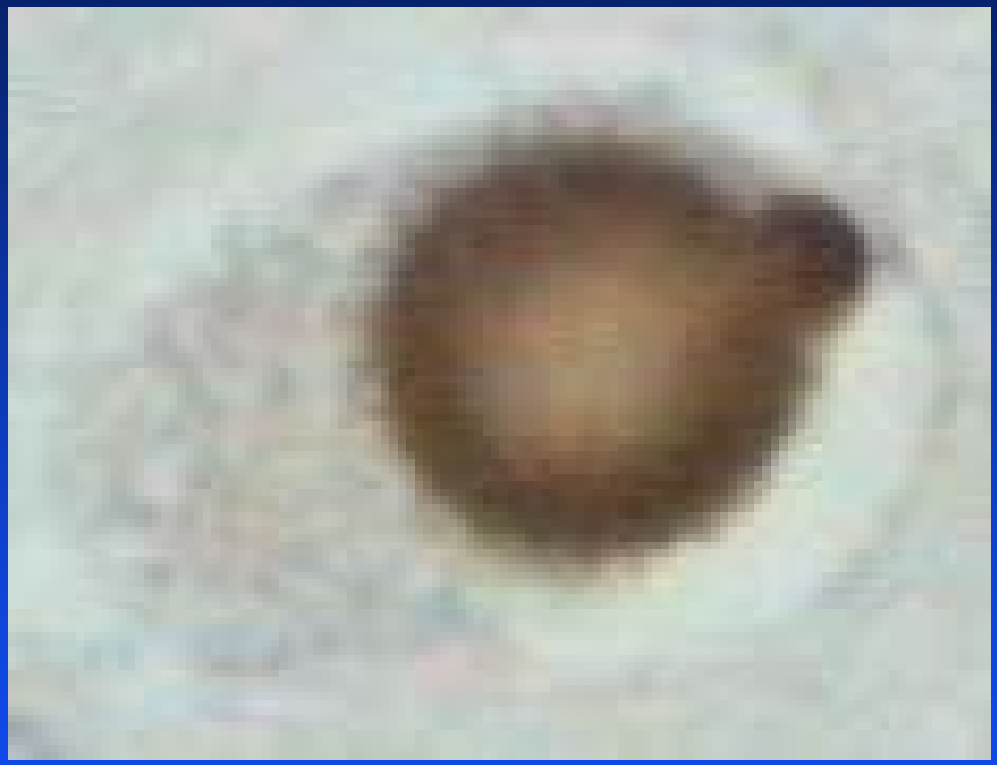
REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Parkinson's Disease/Dementia With Lewy Bodies/ Lewy Body Disease Phenomenology:

LBD Phenomenology

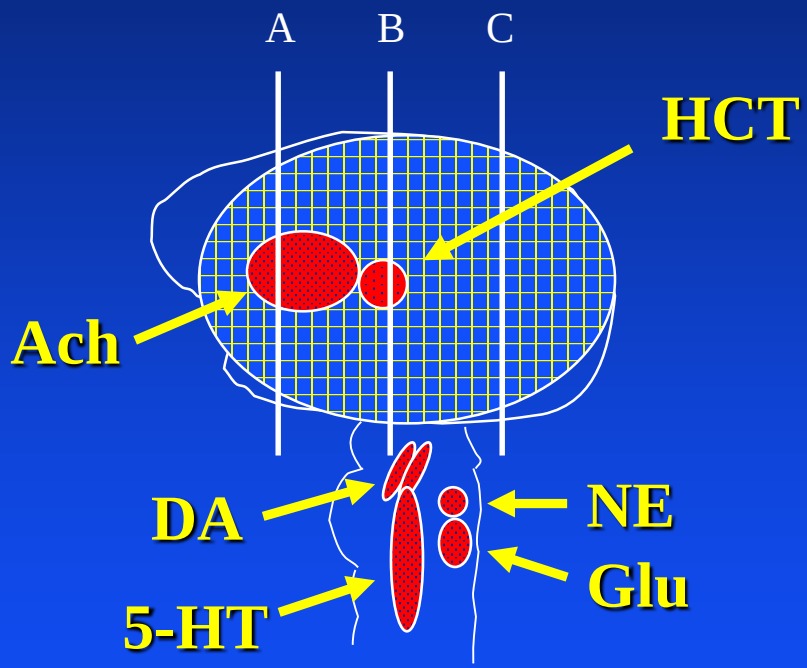
Lewy Body Disease

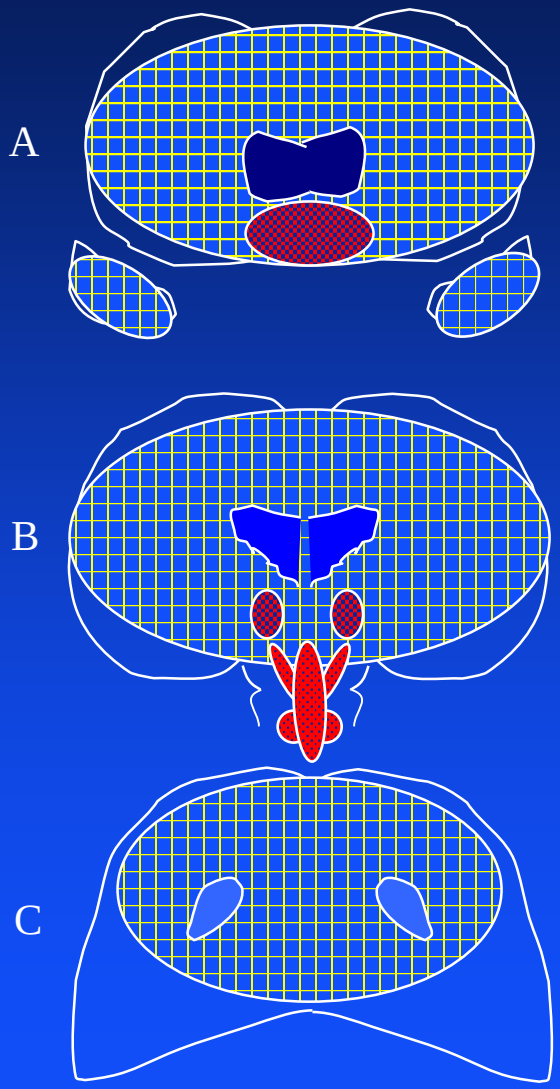




Lewy body

Lewy Body Disease





Lewy Body Disease

cognitive impairment

visual hallucinations

hypersomnia

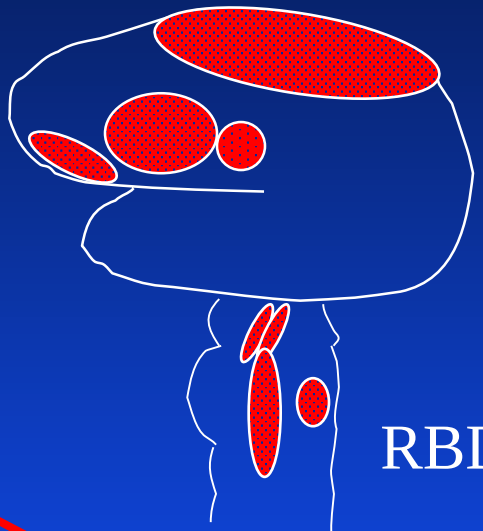
parkinsonism

sleep fragmentation

depression

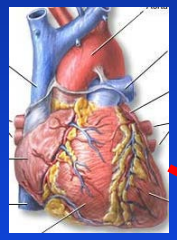
anxiety

anosmia

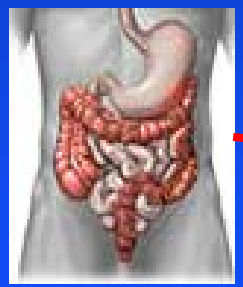


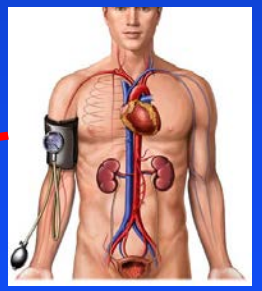
RBD

dysrythmia



constipation

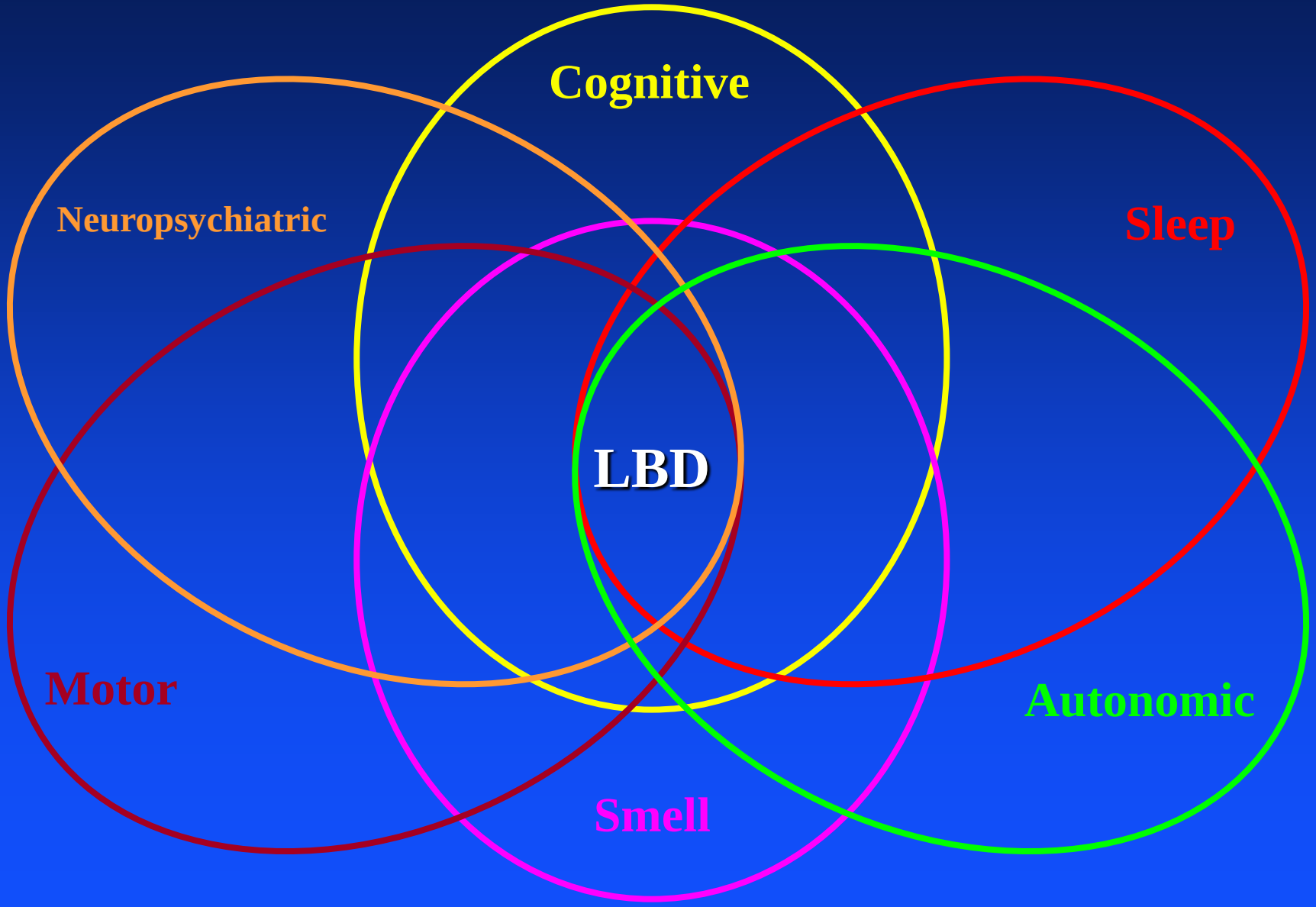




orthostatic hypotension

erectile dysfunction
urinary dyscontrol

Lewy Body Disease



REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Parkinson's Disease/Dementia With Lewy Bodies/ Lewy Body Disease Phenomenology:

The PD-Predominant Phenotype

The DLB-Predominant Phenotype

Lewy Body Disease
Major Clinical Phenotypes

Motor

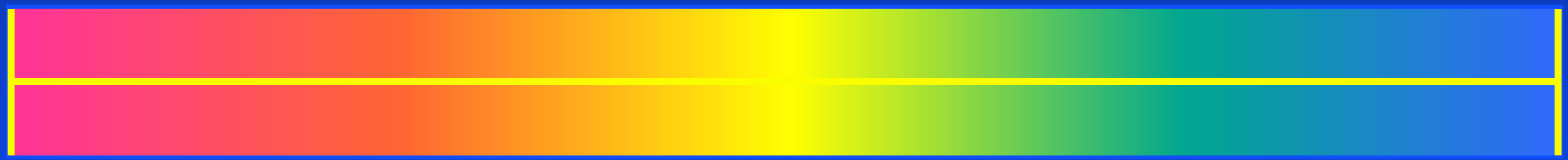
Normal

Mild Parkinsonian Signs

Parkinson's Disease

Parkinson's Disease + Dementia

Nl | MPS | PD | PD + MCI | PDD



Nl | MCI | DLB

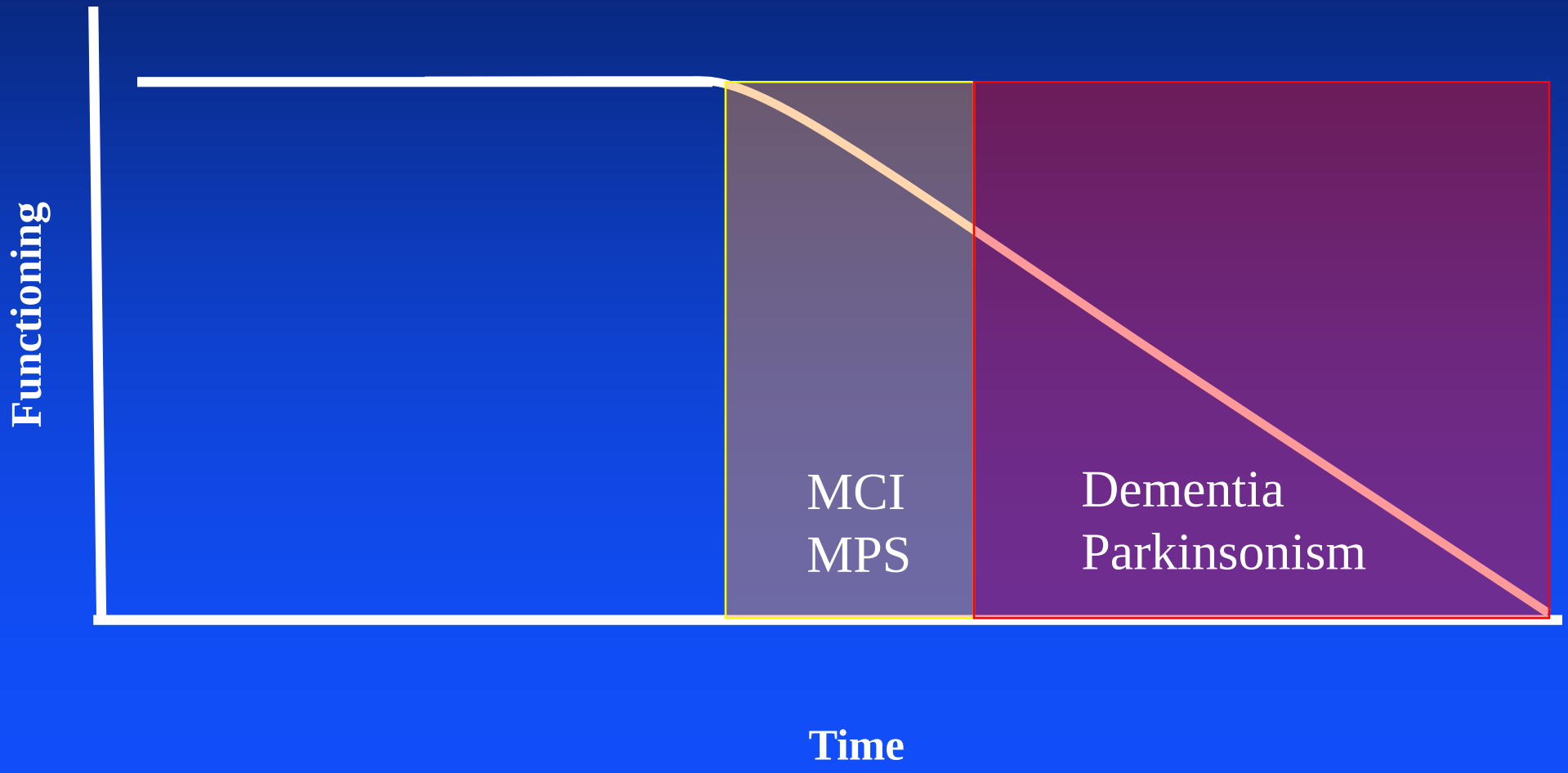
Cognitive

Normal

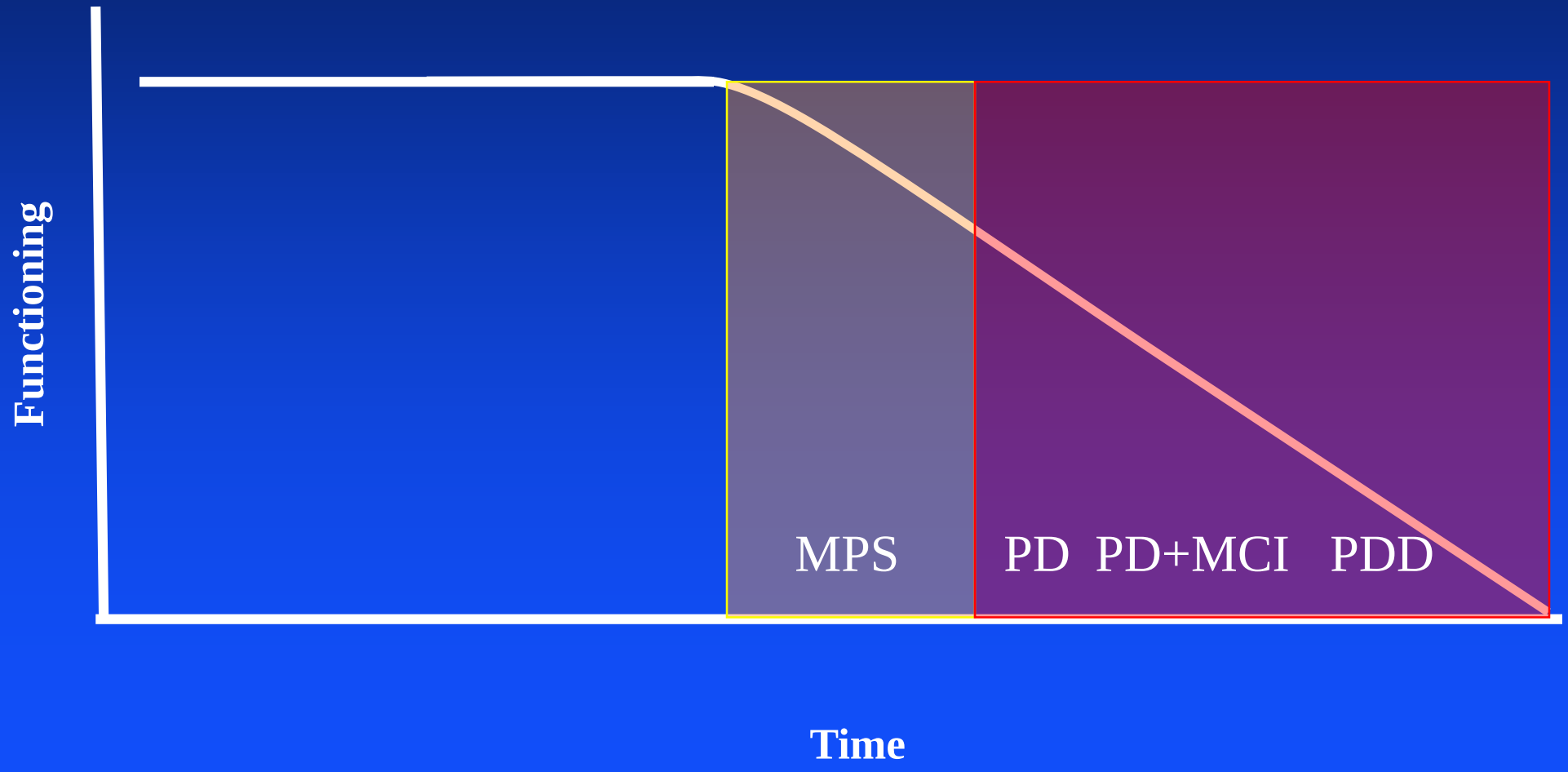
Mild Cognitive Impairment

Dementia with Lewy Bodies

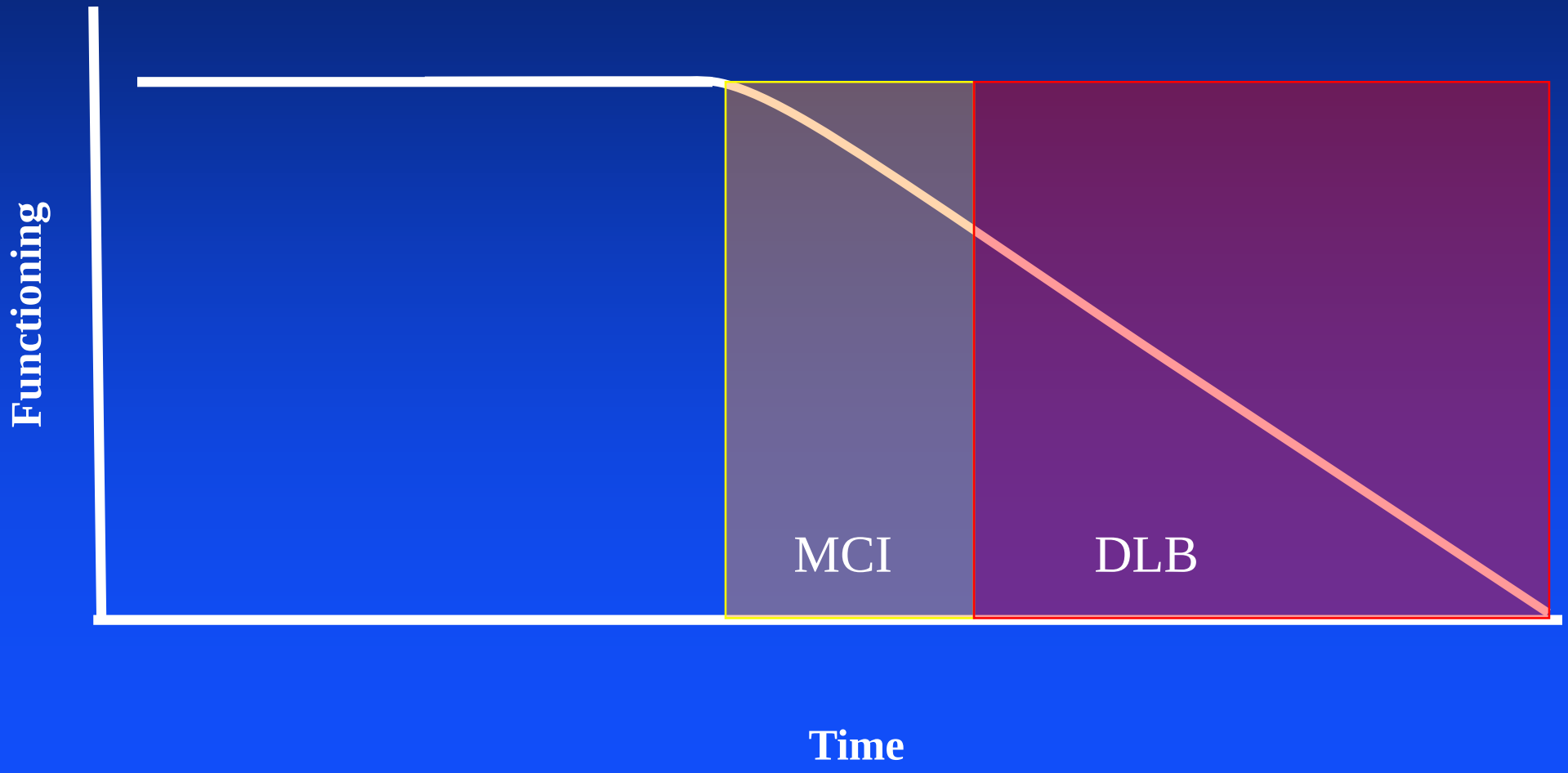
Lewy Body Disease



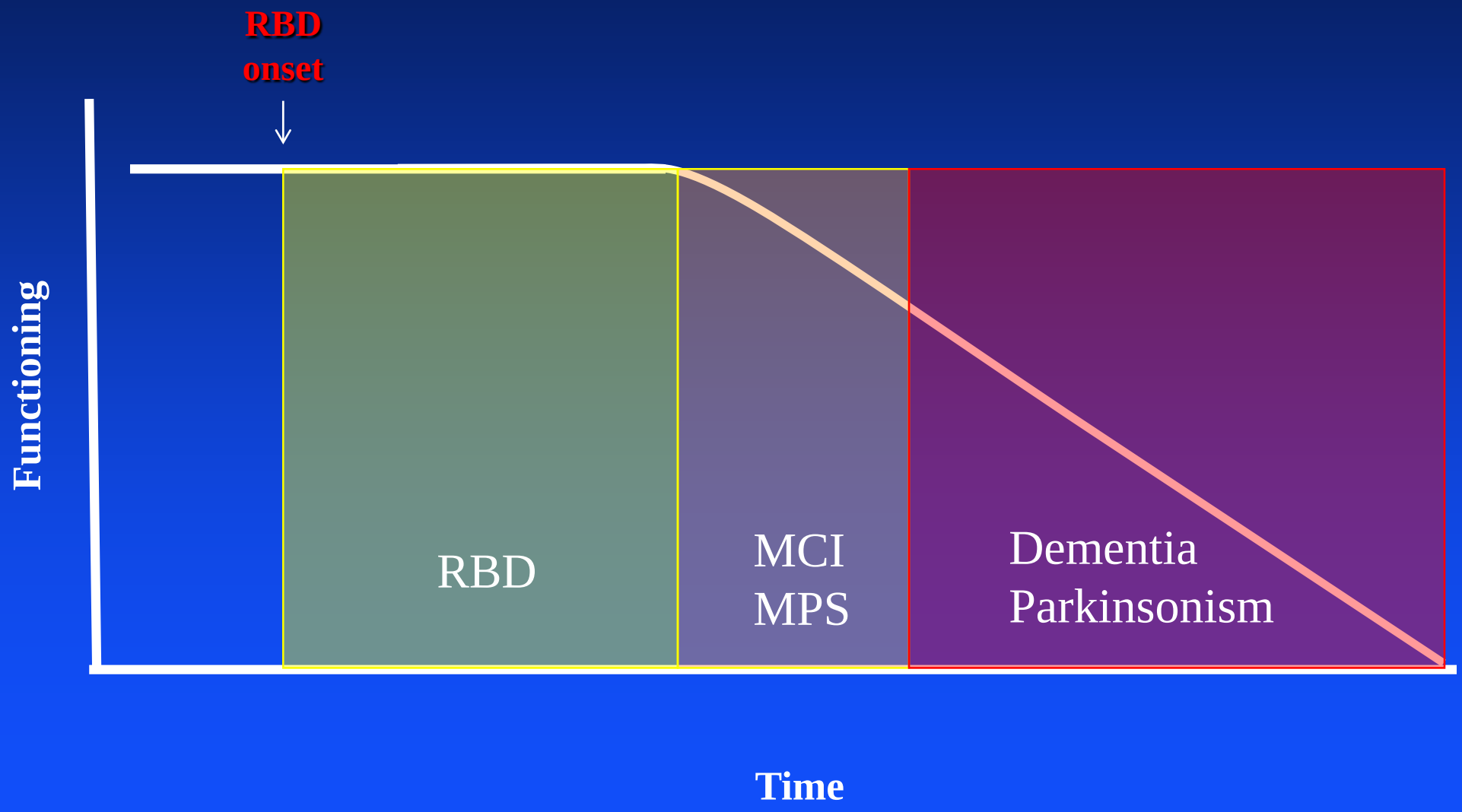
Lewy Body Disease
Parkinson's Disease-Predominant Phenotype



Lewy Body Disease
Dementia with Lewy Bodies-Predominant Phenotype



Lewy Body Disease



REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Idiopathic RBD Analyses

Retrospective Analyses

Idiopathic RBD

Definition

• Presence of RBD in the absence of any other obvious neurologic signs/symptoms or disorders

Prevalence

• 0.5% to 9% (depending on population studied)

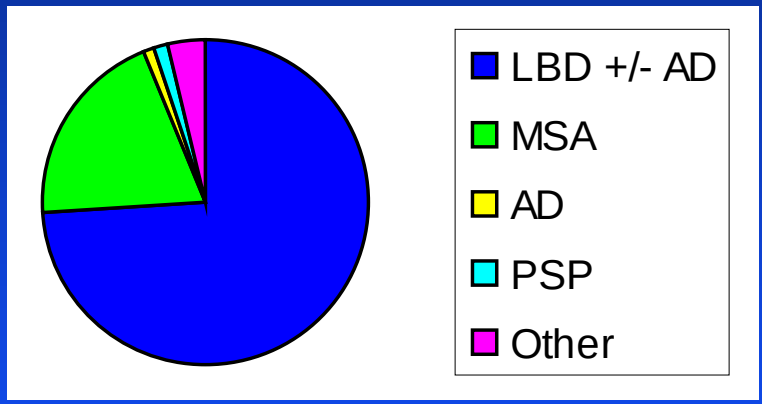
Idiopathic RBD
Retrospective Analyses

RBD preceded neurodegenerative syndrome (n=170):

>50% of cases

- mean – 10 years
- range – 1-61 years

Pathology in PSG proven cases (n=82):



Boeve BF et al, Sleep Med 2013

Idiopathic RBD
Retrospective Analyses

Salients Points

Analyses have repeatedly shown that when RBD is associated with a neurodegenerative disease:

• The neurodegenerative syndrome is almost always (>95%) within the presumed synucleinopathy spectrum (eg, PD, DLB, MSA, PAF)

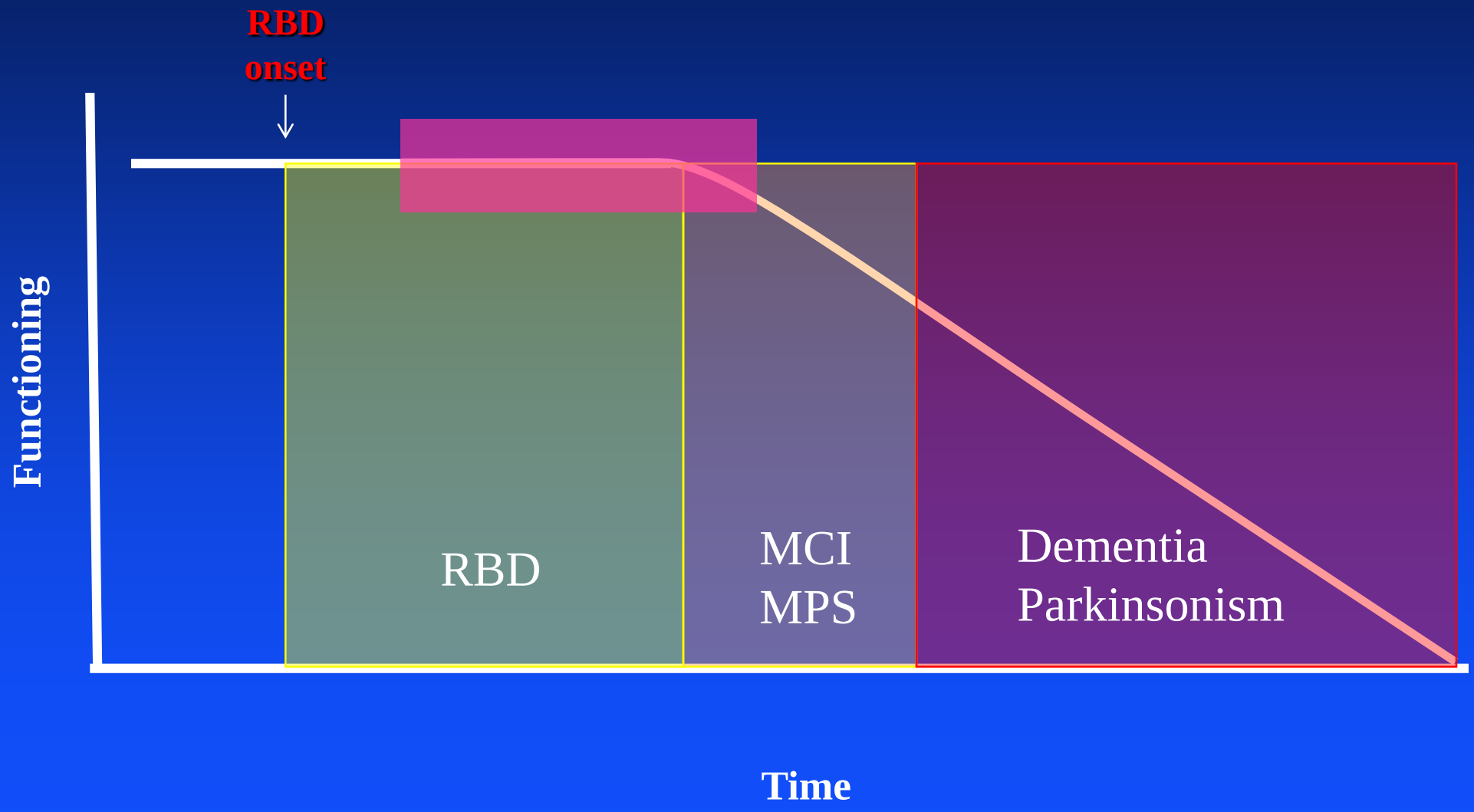
• RBD usually precedes the onset of cognitive impairment, parkinsonism or autonomic dysfunction by years or decades

REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Idiopathic RBD Analyses

Cross-Sectional Correlative Analyses

Lewy Body Disease



Idiopathic RBD
Correlative Analyses

Abnormalities demonstrated on measures of:

- Olfaction
- Color vision
- Motor functioning
- Mood
- Anxiety
- Apathy

- Neuropsychological functioning
- Autonomic testing

- EEG

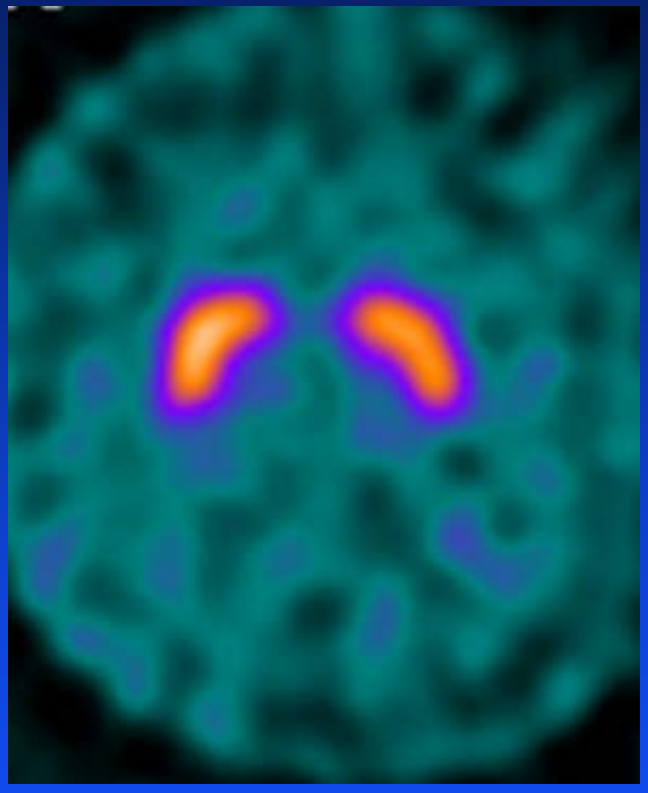
- MRI/MRS/fMRI/DTI

- MIBG

- Perfusion SPECT
- DaTscan
- FDG-PET
- FD-PET

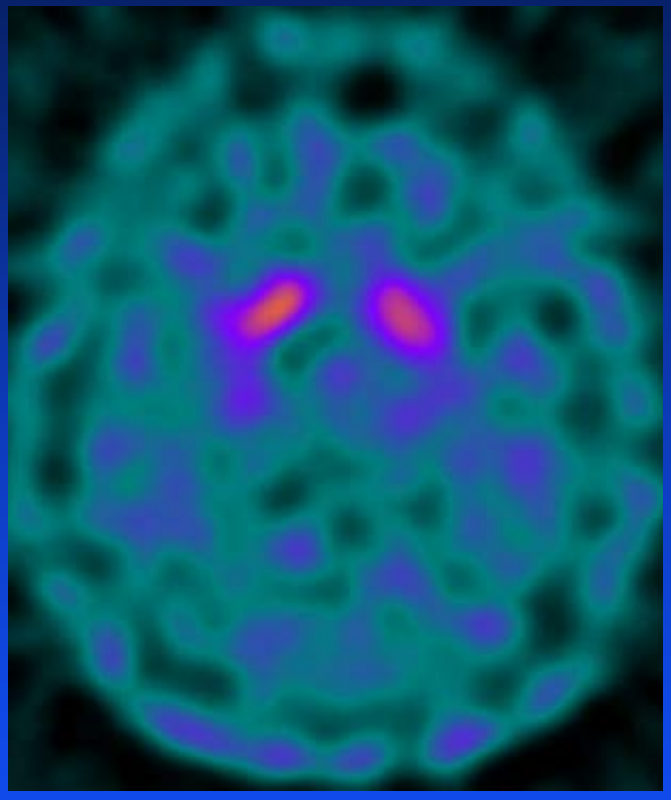
Numerous investigators

DaTscan
Correlative Analyses



AD

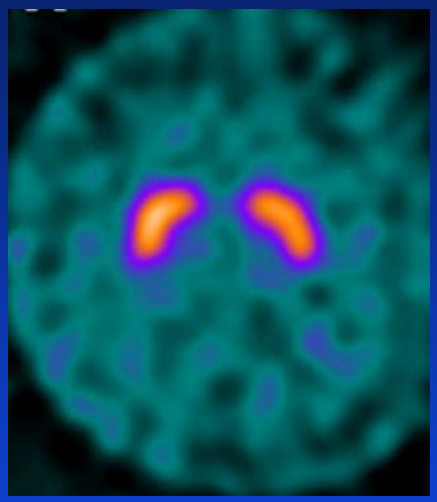
mPOR
2.41



RBD + DLB

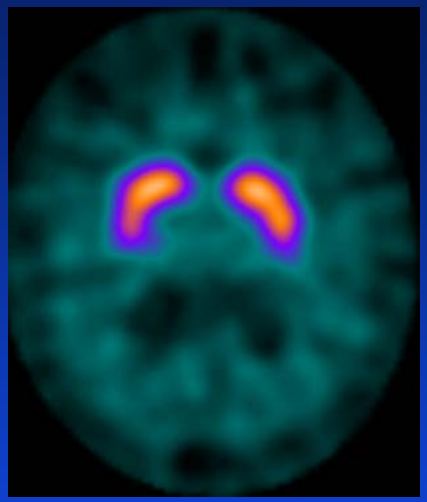
mPOR
1.01

DaTscan
Correlative Analyses



AD

mPOR
2.41



aMCI

mPOR
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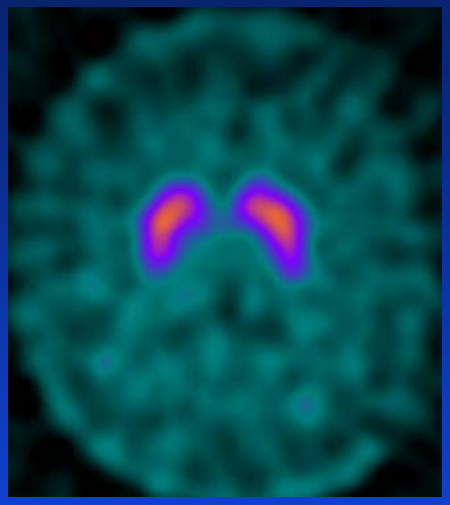
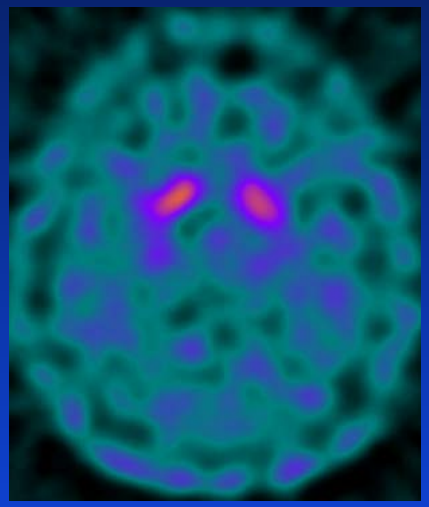


RBD+
naMCI

mPOR
2.1

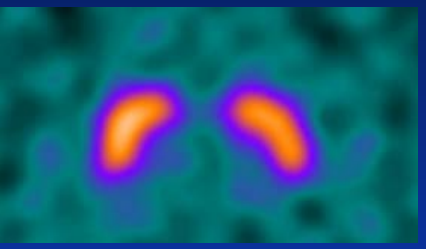


RBD
+DLB

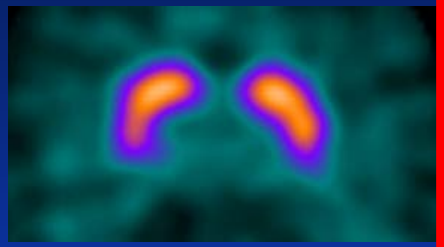
mPOR
1.01

Boeve et al, AAN 2013

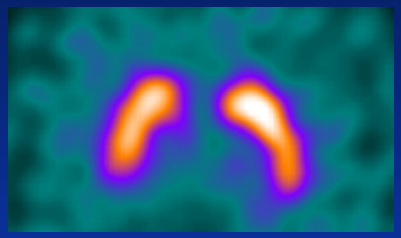
DaTscan
Correlative Analyses



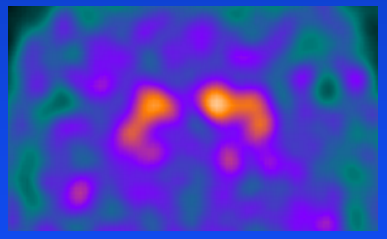
AD
mPOR
2.41



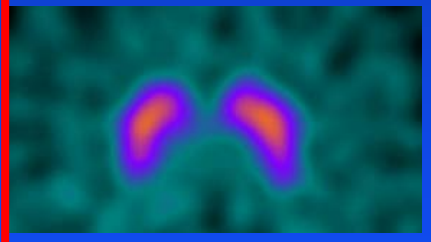
aMCI
mPOR
2.31



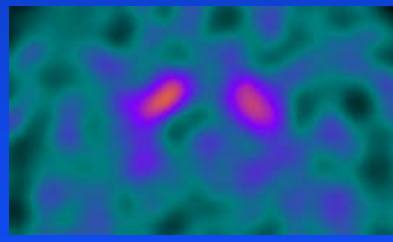
iRBD
mPOR
2.49



iRBD
mPOR
1.29



RBD+naMCI
mPOR
2.1



RBD+DLB
mPOR
1.01

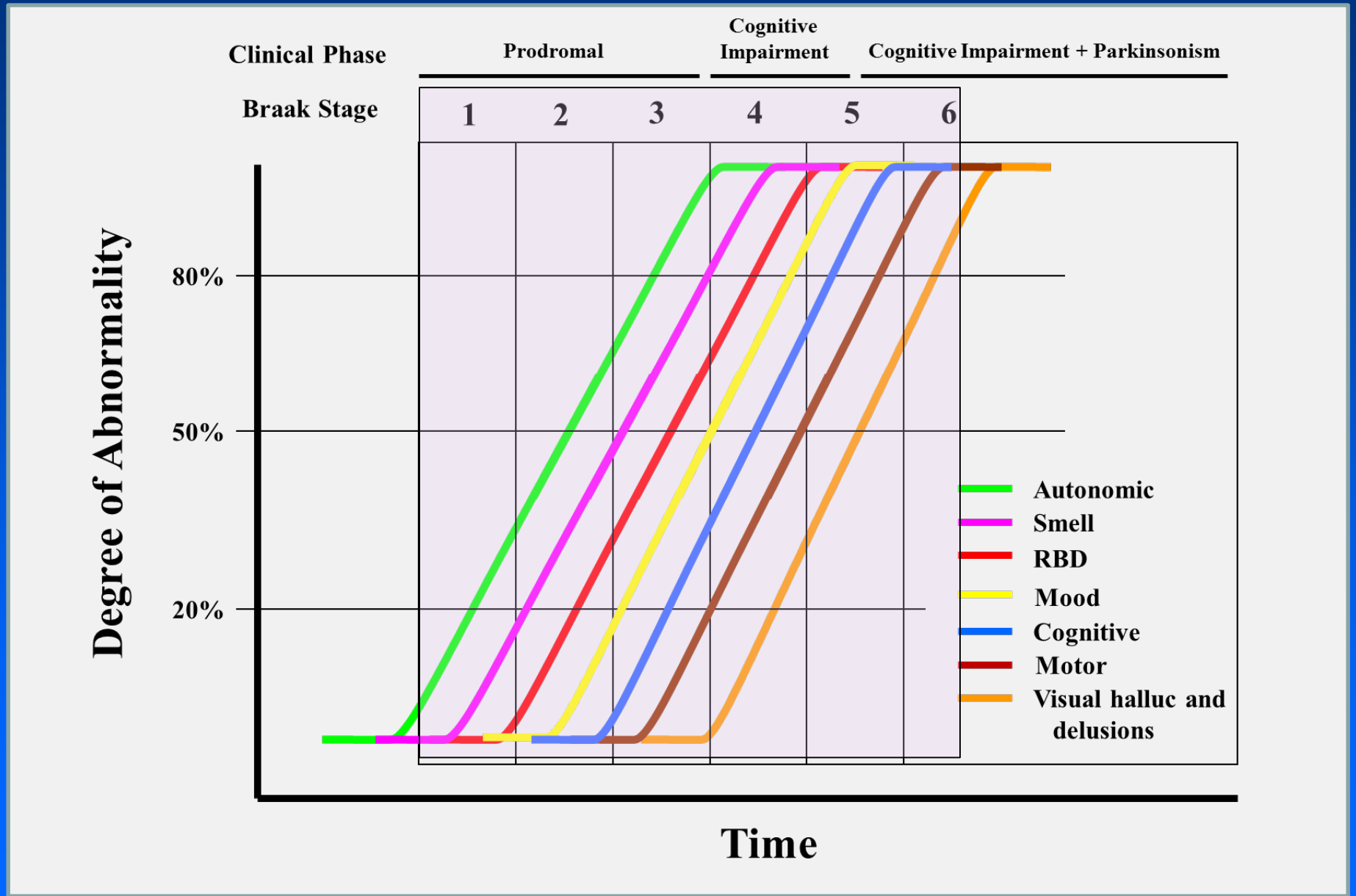
Idiopathic RBD
Correlative Analyses

Salient Points

- A significant proportion of iRBD patients have demonstrable abnormalities on 1 or more measures

- Abnormalities on these measures are most consistent with early/evolving Lewy body disease

Theoretical Evolution of Clinical Manifestations According to Braak Stage in the Prototypical DLB Phenotype of Lewy Body Disease

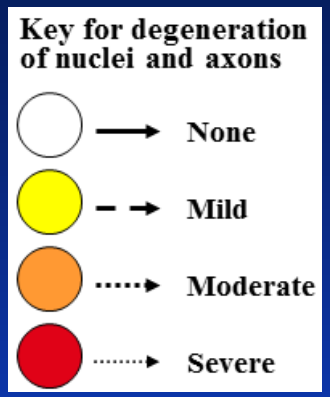


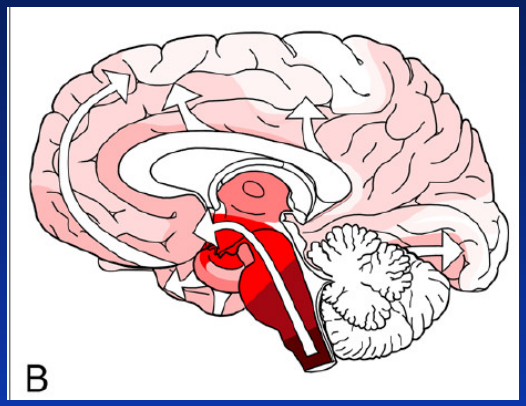
Parkinson's Disease/Lewy Body Disease
Braak Staging Scheme

	Braak stage					
	1	2	3	4	5	6
RBD	Nl	+/–	+	++	+++	+++
Smell tests	↓	↓↓	↓↓	↓↓↓	↓↓↓	↓↓↓
Autonomic tests	↓	↓↓	↓↓	↓↓	↓↓↓	↓↓↓
Motor tests	Nl	Nl	+/–	↓	↓↓	↓↓↓
Neuropsych tests	Nl	Nl	+/–	↓	↓↓	↓↓
Electrophysiology						
EMG atonia during REM sleep	Nl	↓	↓↓	↓↓↓	↓↓↓	↓↓↓
EEG activity	Nl	Nl	↓	↓↓	↓↓↓	↓↓↓
Imaging						
MIBG	↓	↓	↓↓	↓↓↓	↓↓↓	↓↓↓
DaTscan or FD-PET	Nl	Nl	↓	↓↓	↓↓↓	↓↓↓
MRI or MRS or TS changes	Nl	Nl	↓	↓↓	↓↓↓	↓↓↓
FDG-PET	Nl	Nl	Nl	↓	↓↓	↓↓↓
Time →						

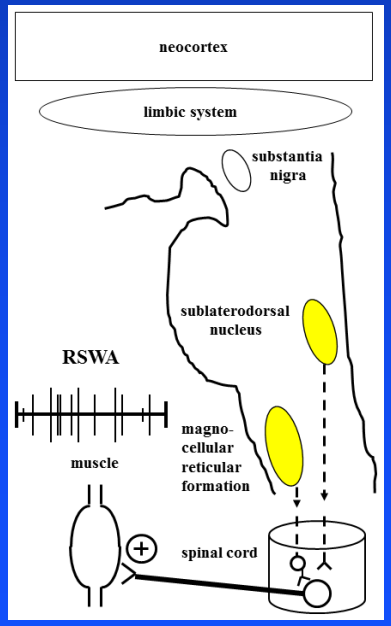
Boeve BF. Lancet Neurology 2013

Framework of RBD Within Braak Staging Scheme

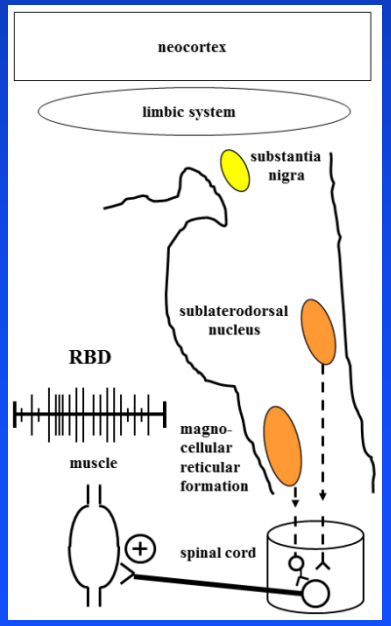




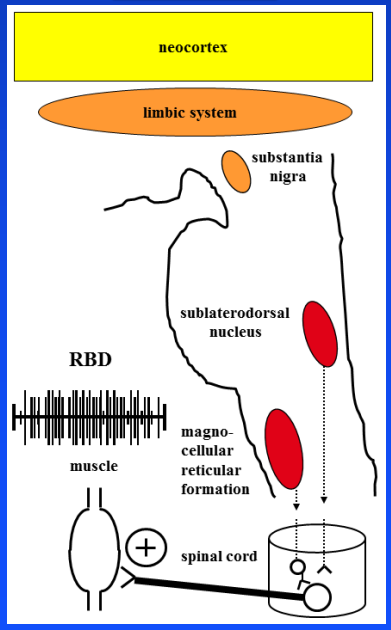
Braak 2



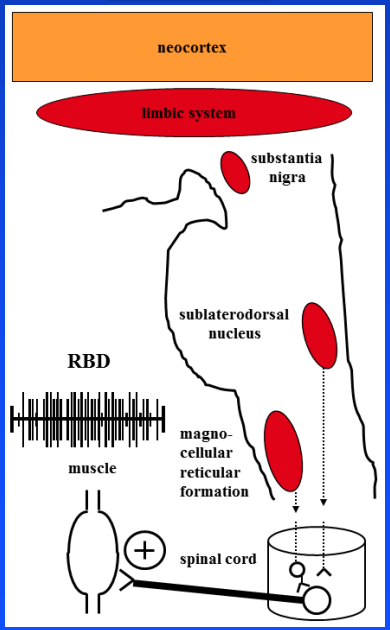
Braak 3



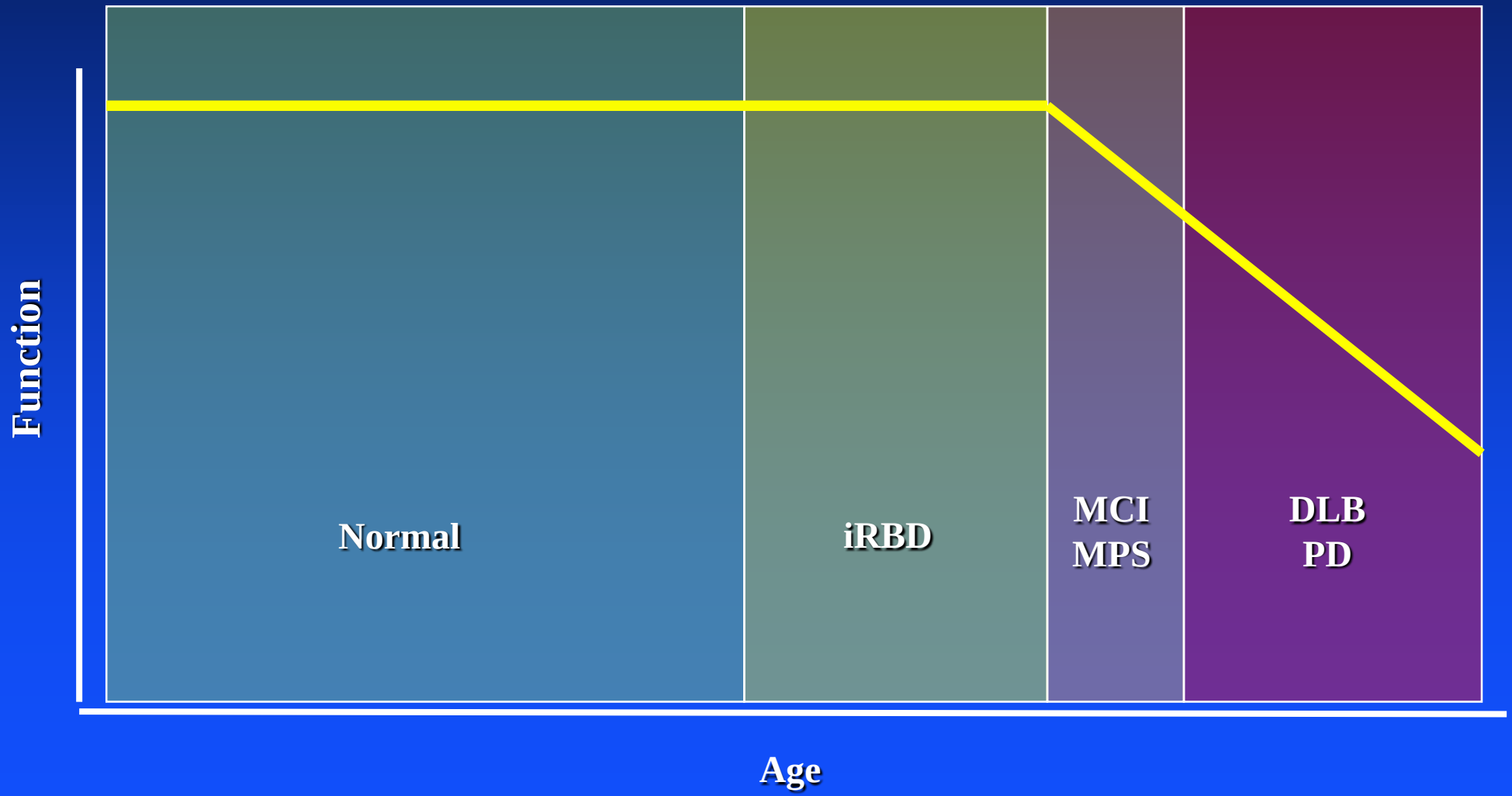
Braak 4



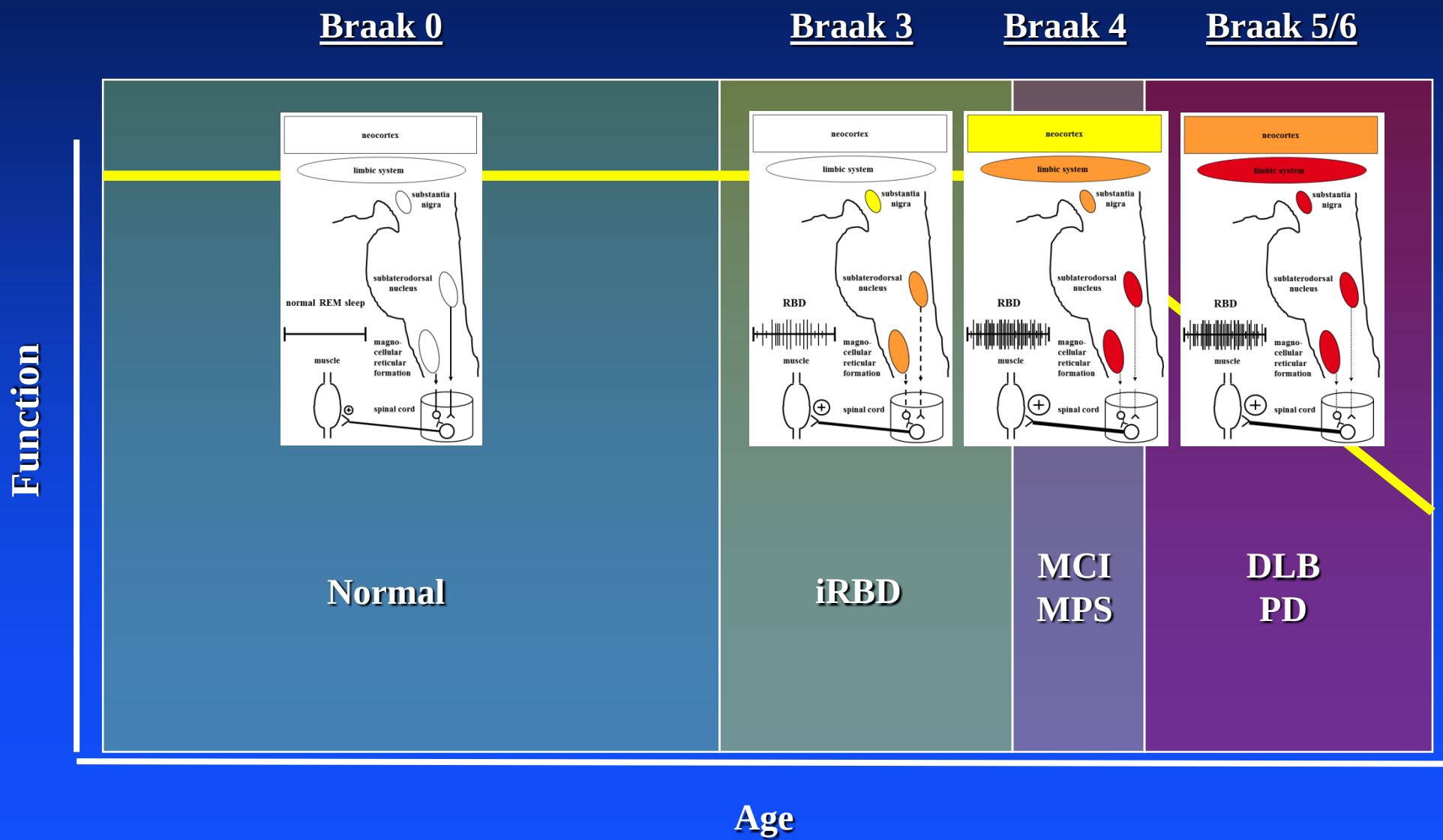
Braak 5



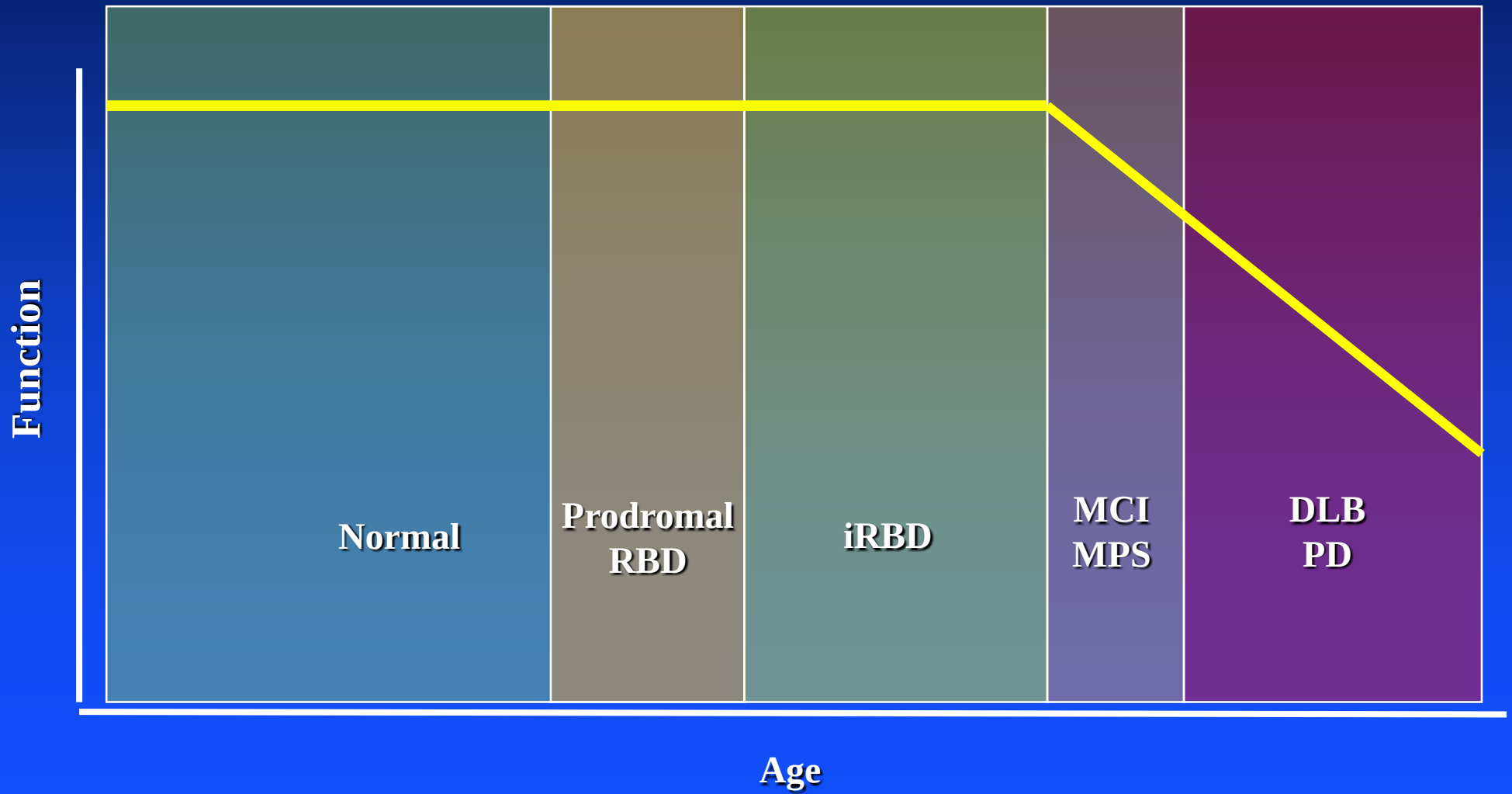
Framework of RBD Within Braak Staging Scheme



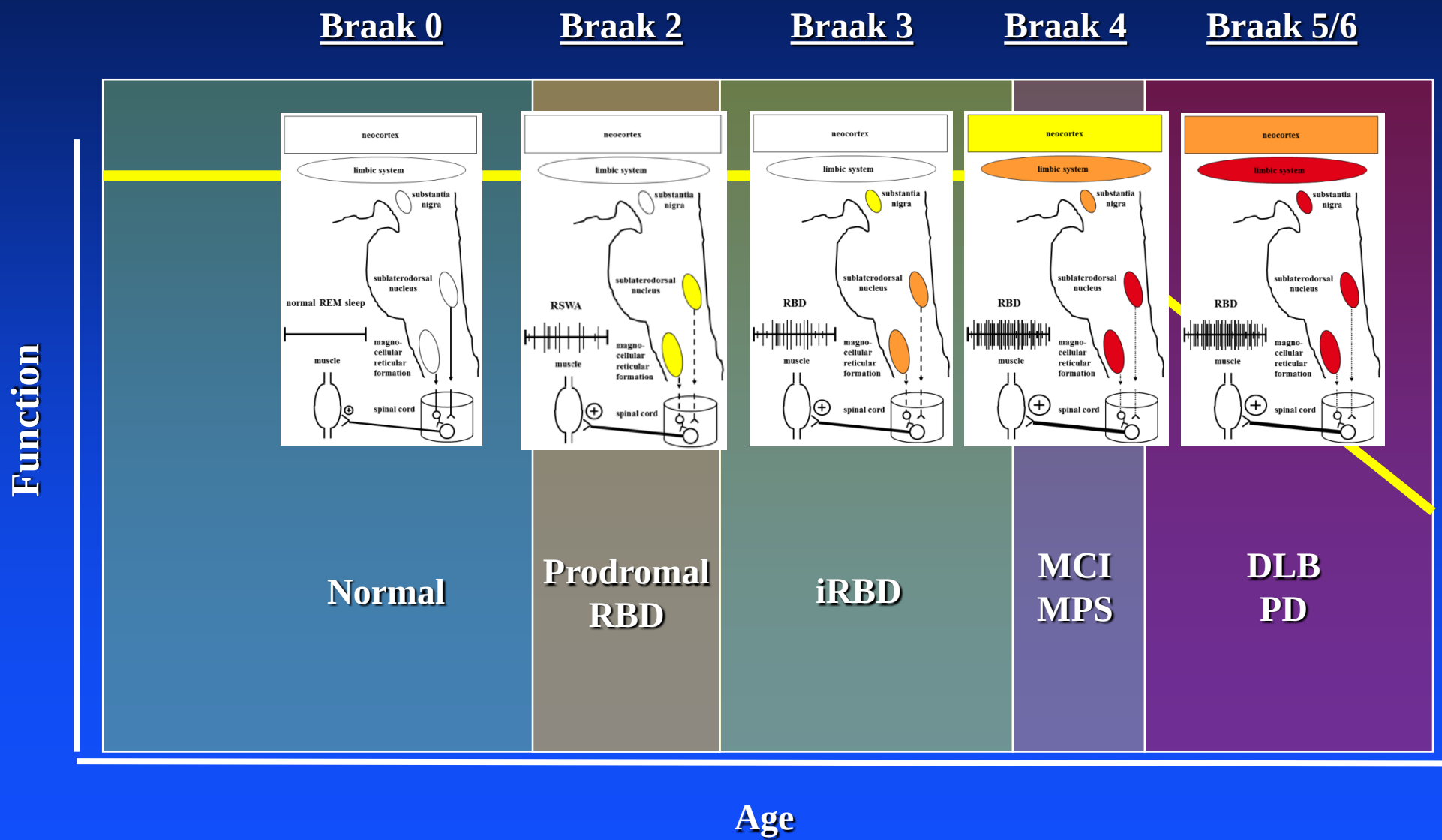
Framework of RBD Within Braak Staging Scheme



Framework of RBD Within Braak Staging Scheme



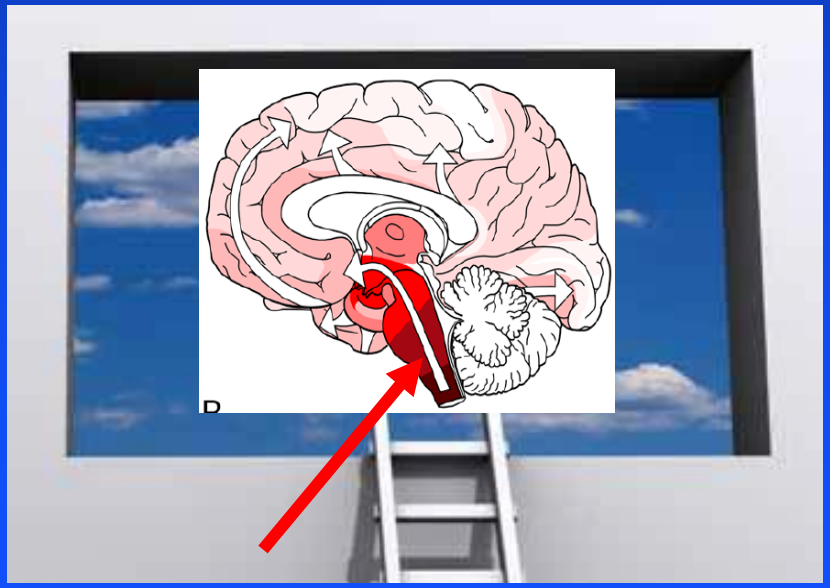
Framework of RBD Within Braak Staging Scheme



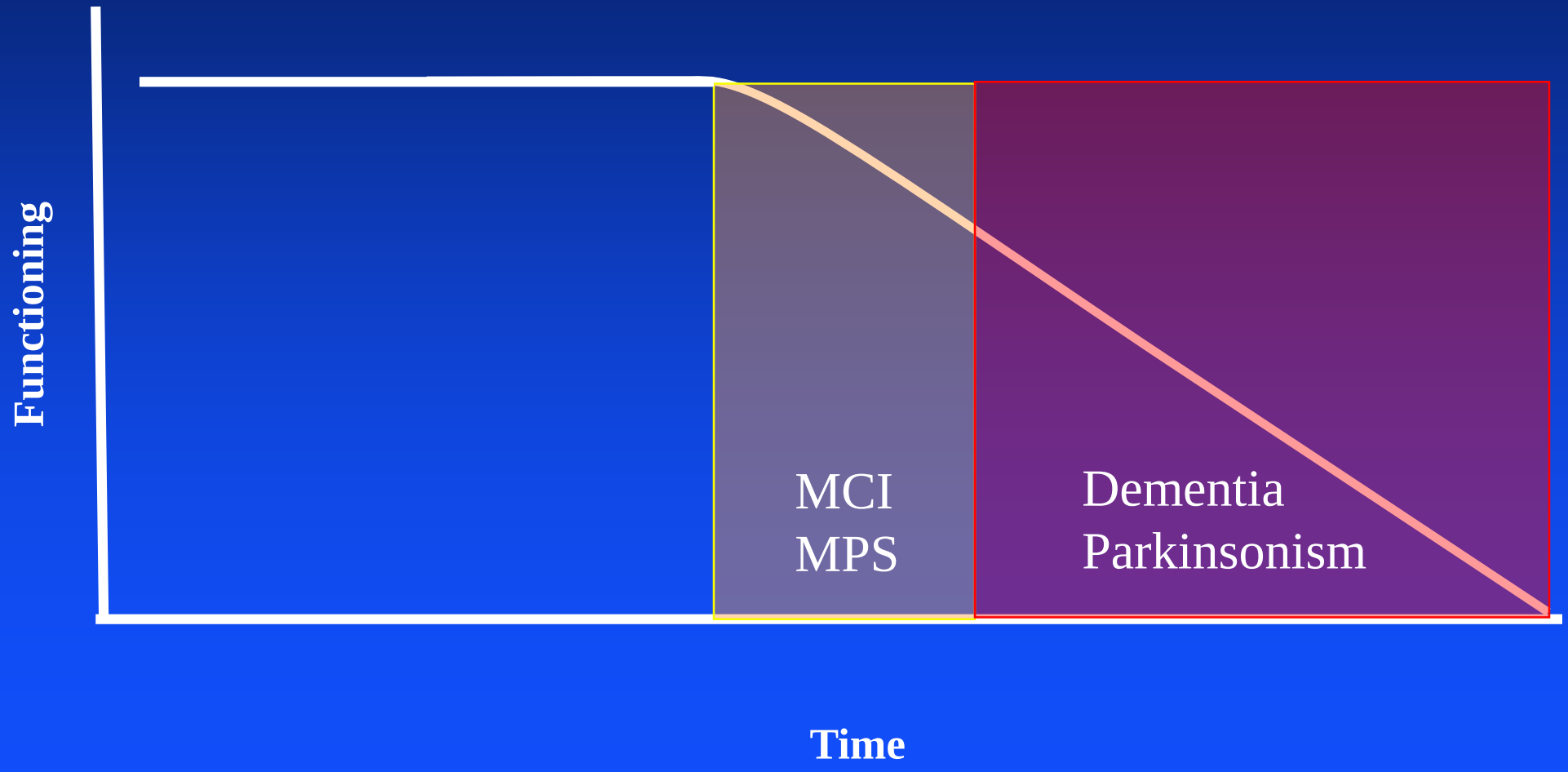
REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Planning for Disease-Modifying Therapies in LBD:

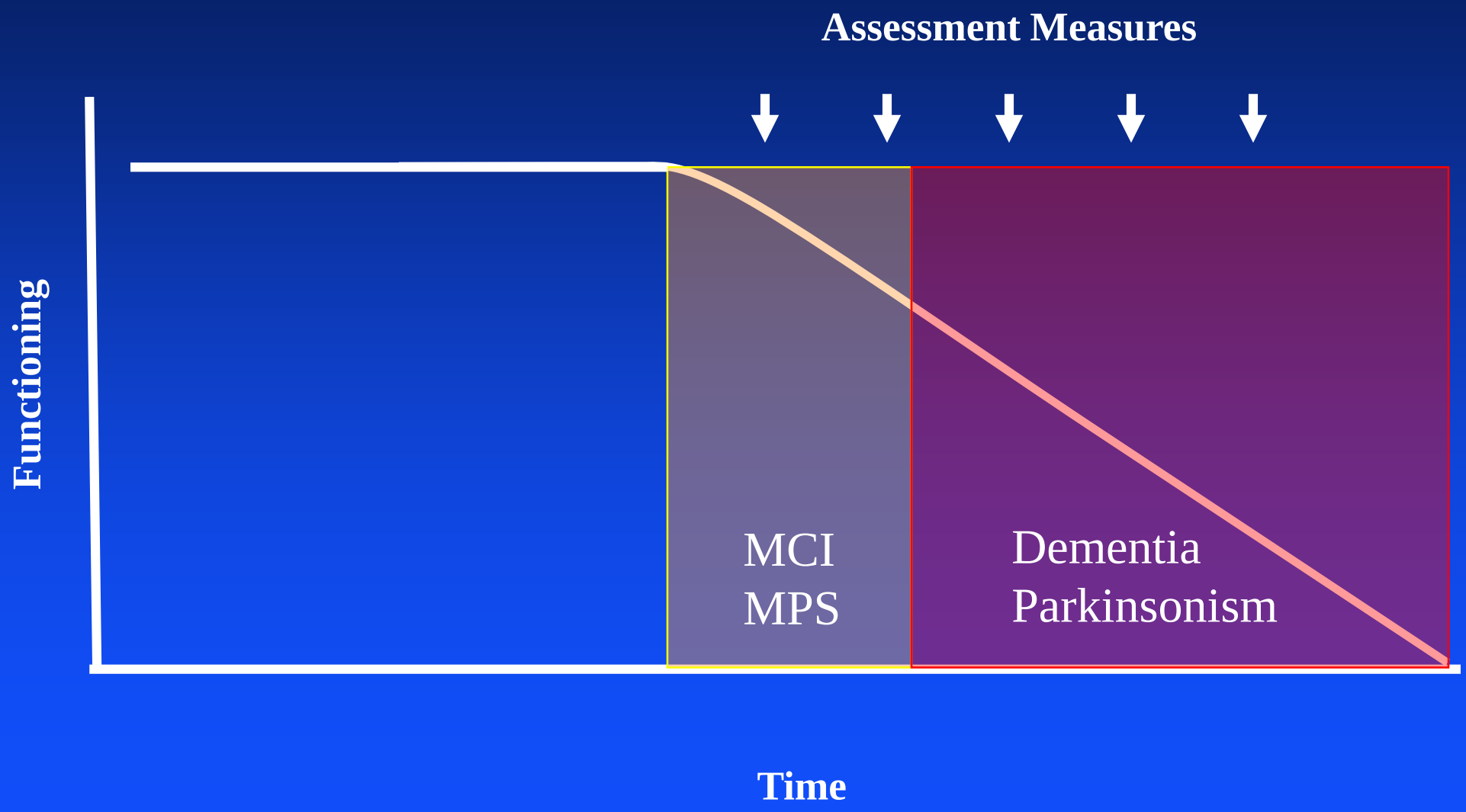
"The RBD Window of Opportunity"



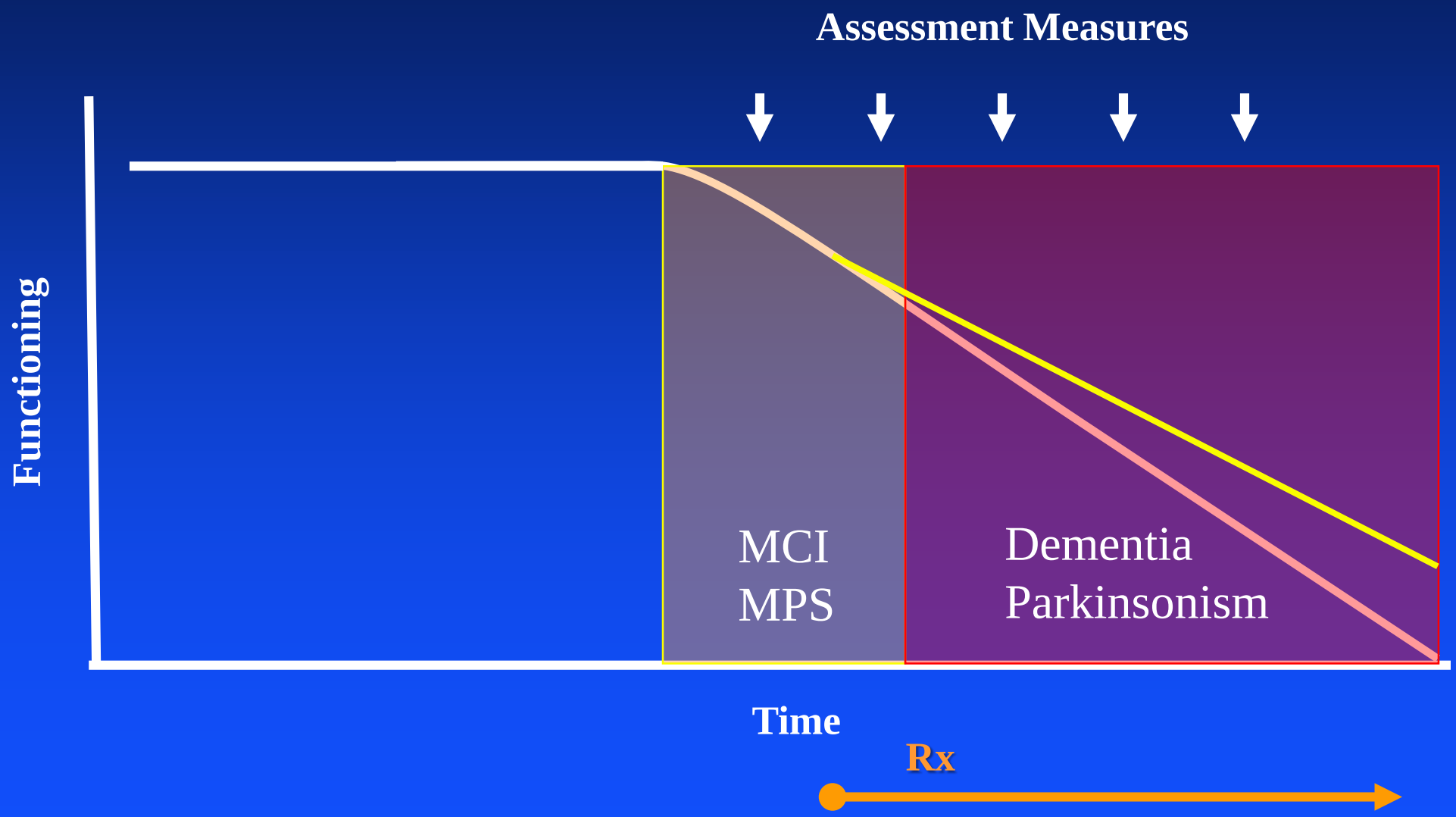
Planning for Disease-Modifying Therapies in LBD



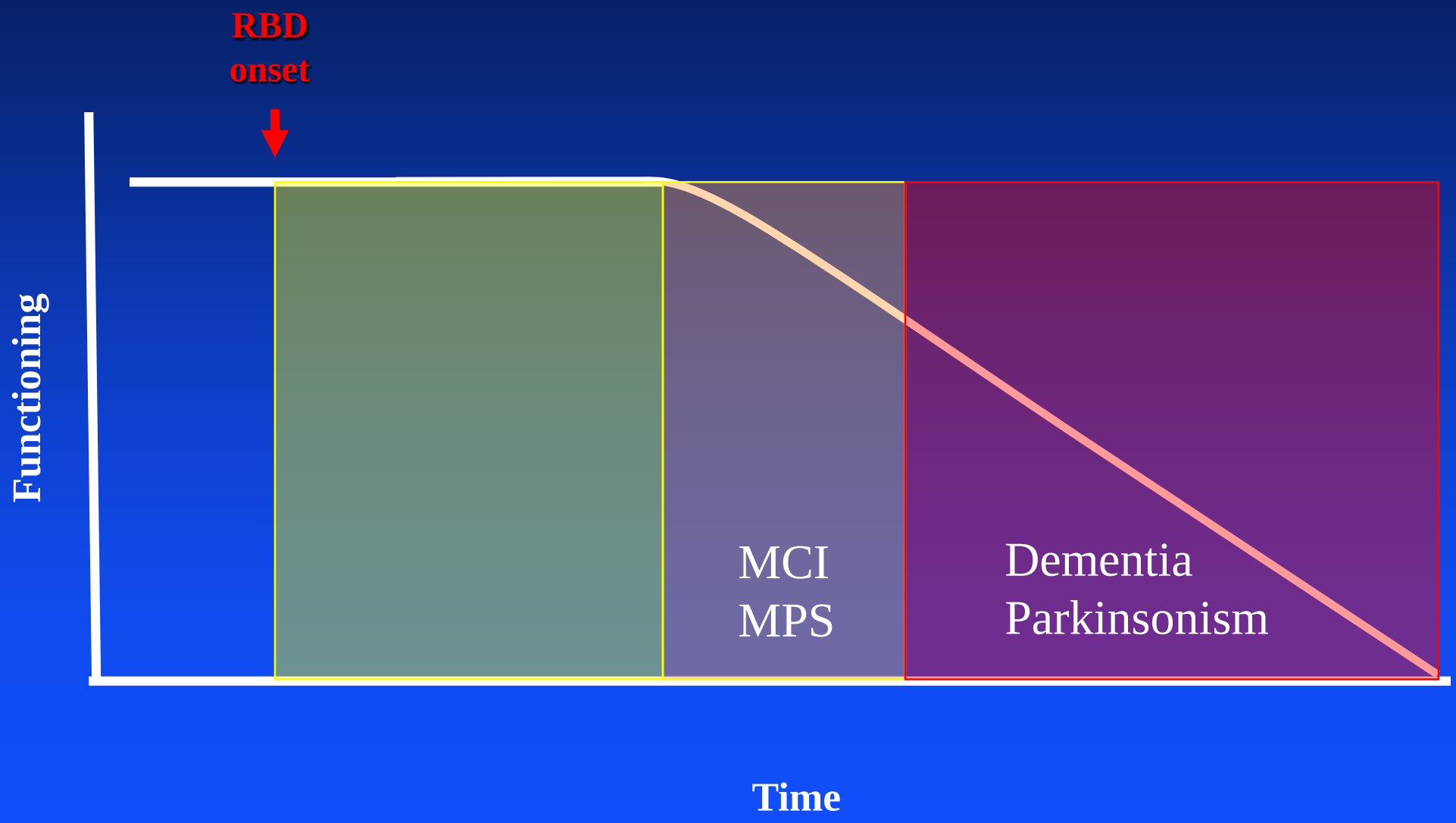
Planning for Disease-Modifying Therapies in LBD



Planning for Disease-Modifying Therapies in LBD



Planning for Disease-Modifying Therapies in LBD



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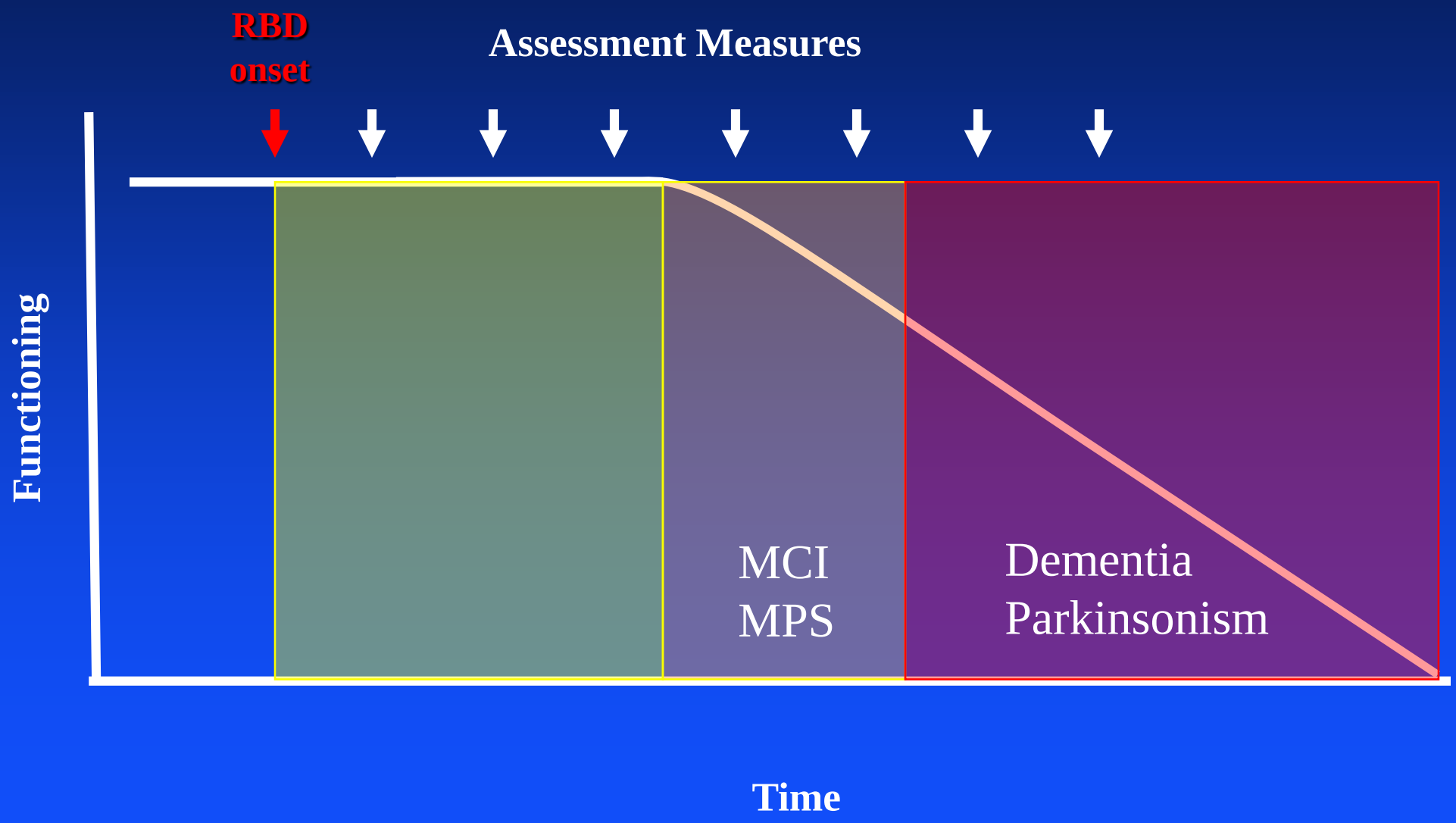


Planning for Disease-Modifying Therapies in LBD

Rapid eye movement sleep behavior disorder: devising controlled active treatment studies for symptomatic and neuroprotective therapy—a consensus statement from the International Rapid Eye Movement Sleep Behavior Disorder Study Group

C.H. Schenck [a,*], J.Y. Montplaisir [b], B. Frauscher [c], B. Hogl [c], J.-F. Gagnon [d], R. Postuma [e], K. Sonka [f], P. Jennum [g], M. Partinen [h], I. Arnulf [i], V. Cochen de Cock [j], Y. Dauvilliers [j], P.-H. Luppi [k], A. Heidbreder [l], G. Mayer [m], F. Sixel-Döring [n,o], C. Trenkwalder [n,p], M. Unger [q,r], P. Young [l], Y.K. Wing [s], L. Ferini-Strambi [t], R. Ferri [u], G. Plazzi [v], M. Zucconi [t], Y. Inoue [w], A. Iranzo [x], J. Santamaria [x], C. Bassetti [y], J.C. Möller [z], B.F. Boeve [aa], Y.Y. Lai [ab], M. Pavlova [ac], C. Saper [ad], P. Schmidt [ae], J.M. Siegel [ab], C. Singer [af], E. St Louis [aa], A. Videnovic [ag], W. Oertel [o]

Sleep Medicine 2013

Assessment Measures

Clinical

- Screening mental status exam (MMSE, MoCA)
- Motor examination (UPDRS)
- Olfactory, color vision

Neuropsychological

- Measure each cognitive domain

Electrophysiologic

- EEG, PSG, MSLT, MWT

Biofluid

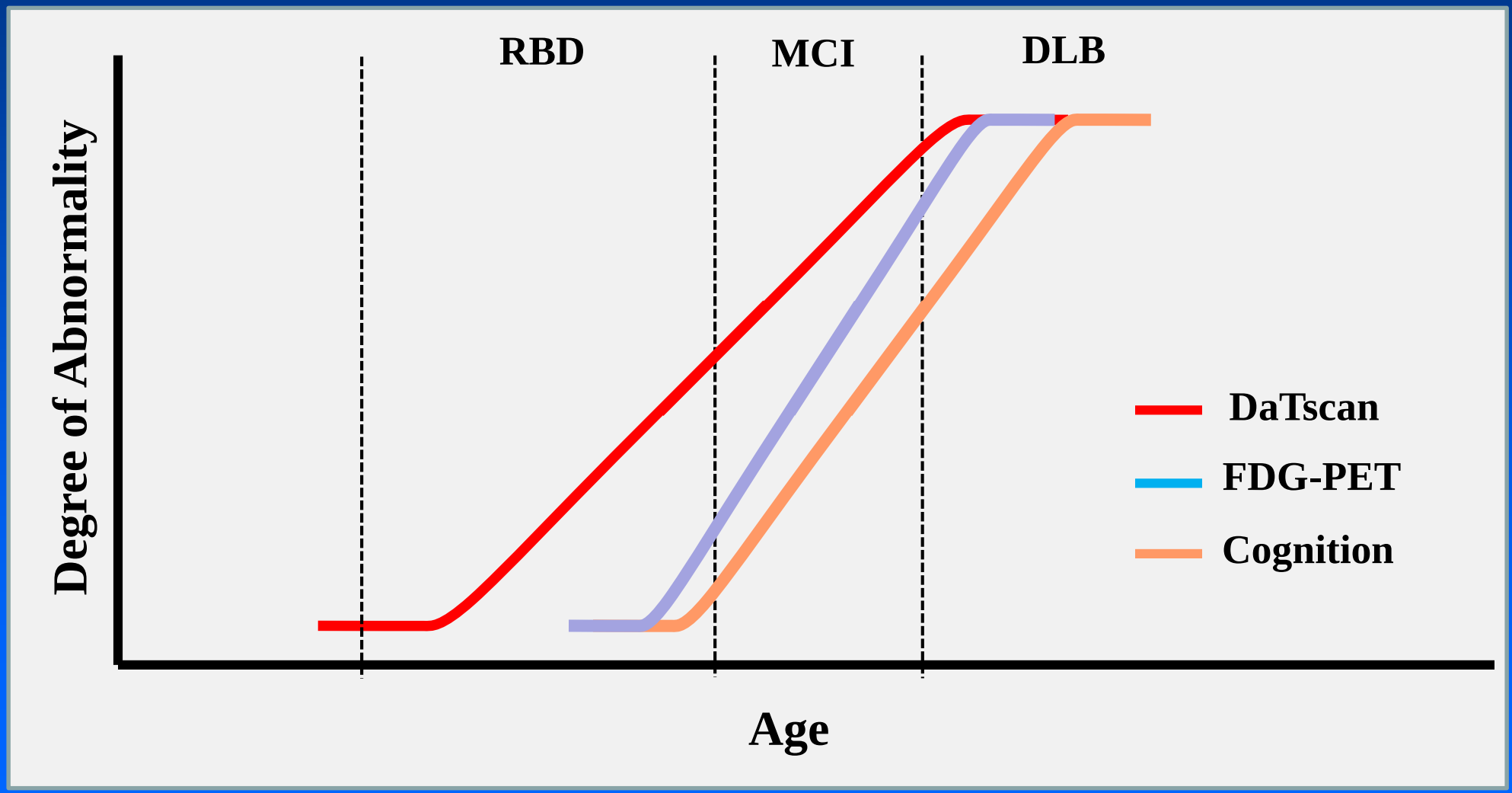
- Blood
- CSF (amyloid, tau, TDP-43, α-synuclein)

Neuroimaging

- MR – MRI, MRS, fMRI, DTI
- PET – FDG, PiB
- SPECT – DaTSCAN, MIBG
- TCS

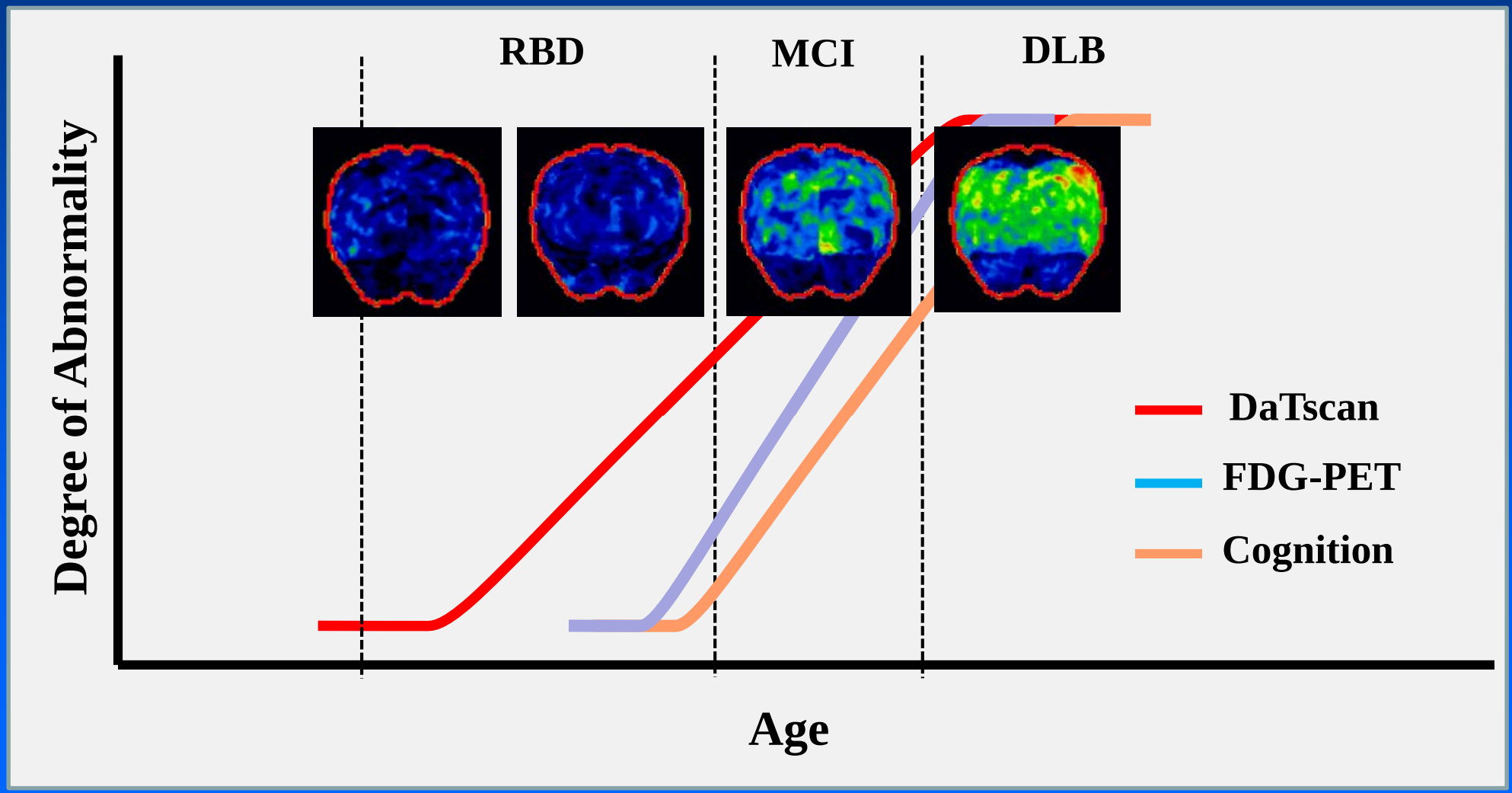
Planning for Disease-Modifying Therapies in LBD

Theoretical Considerations for RBD to MCI to DLB



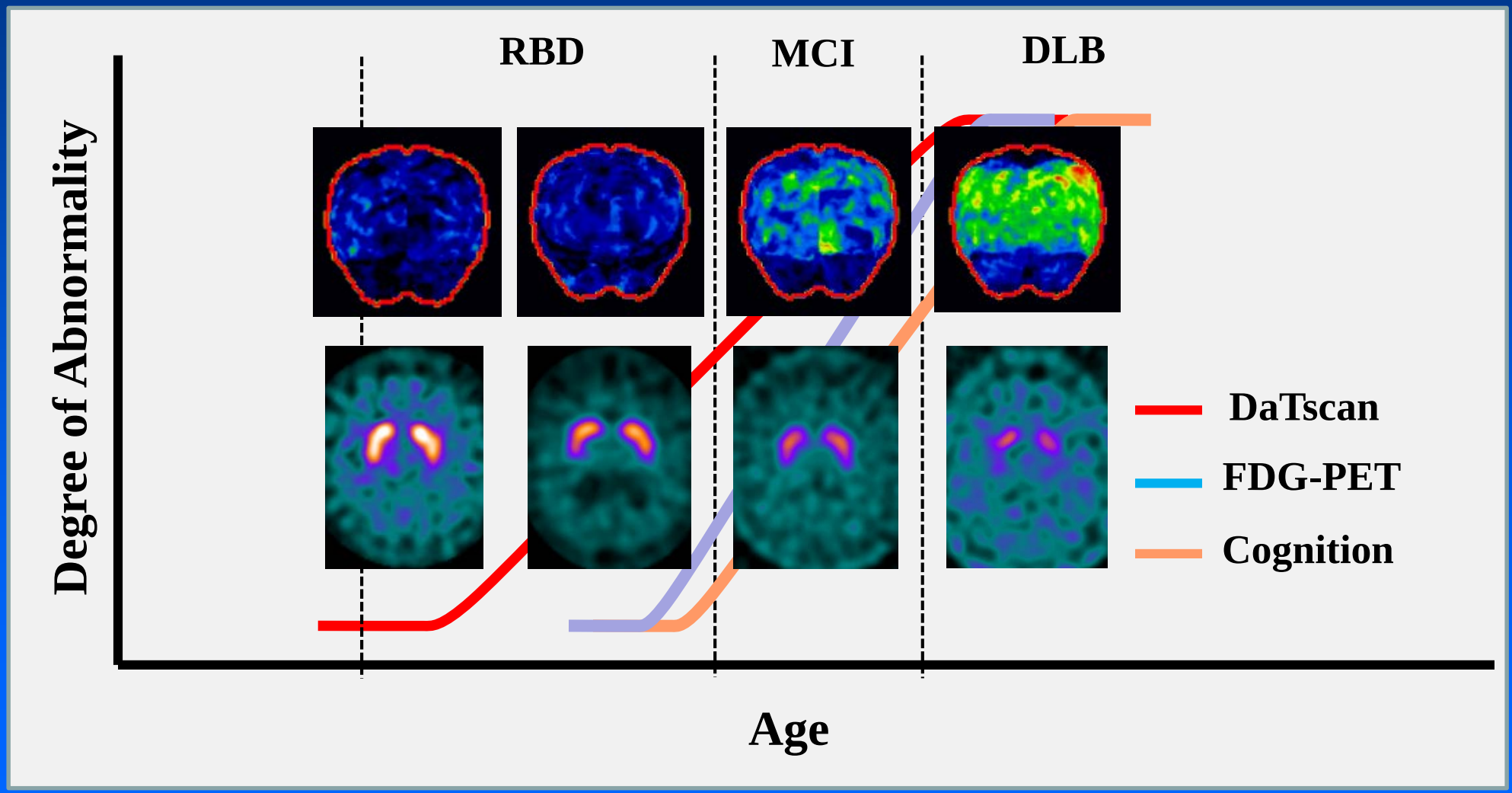
Planning for Disease-Modifying Therapies in LBD

Theoretical Considerations for RBD to MCI to DLB

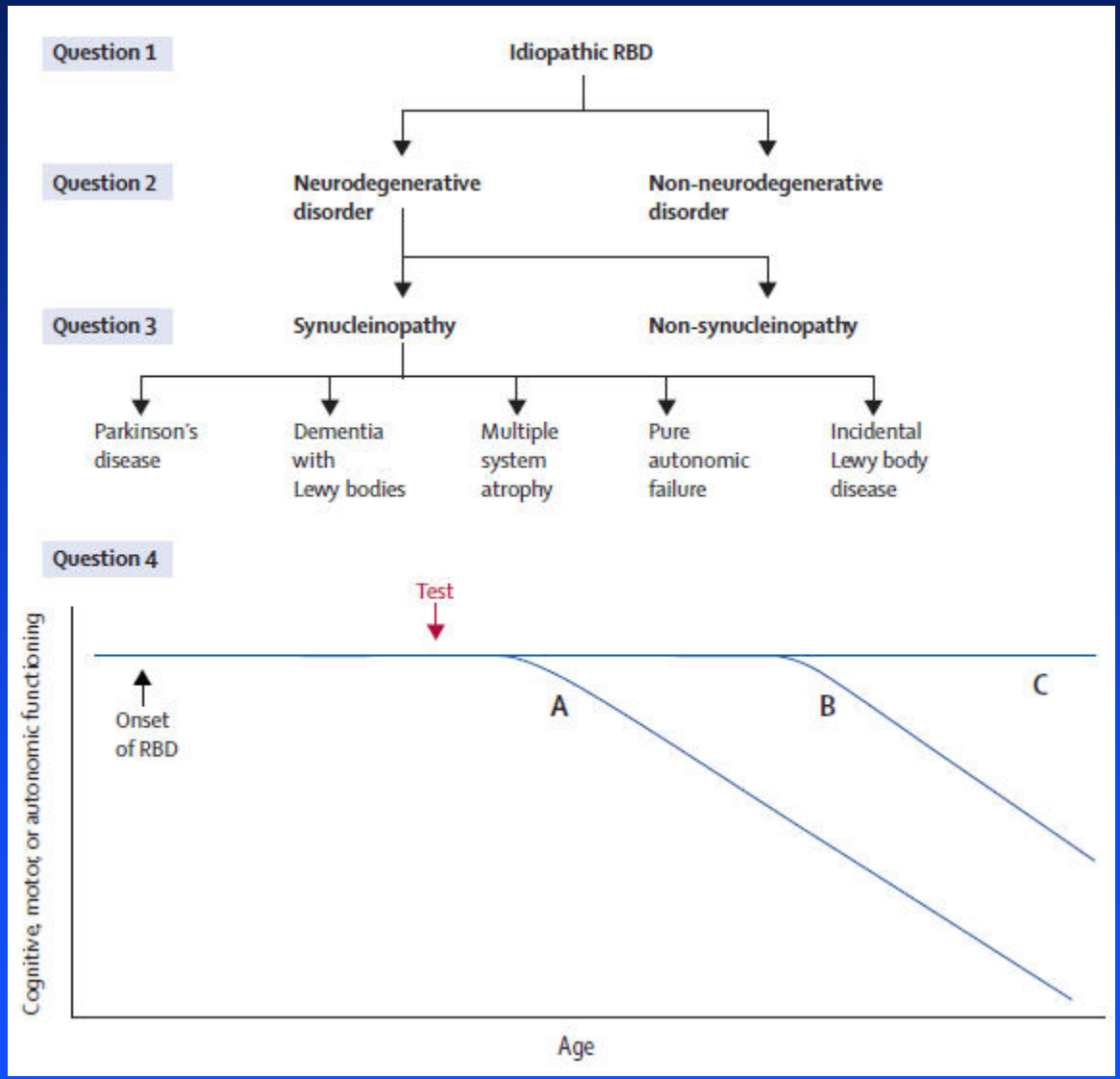


Planning for Disease-Modifying Therapies in LBD

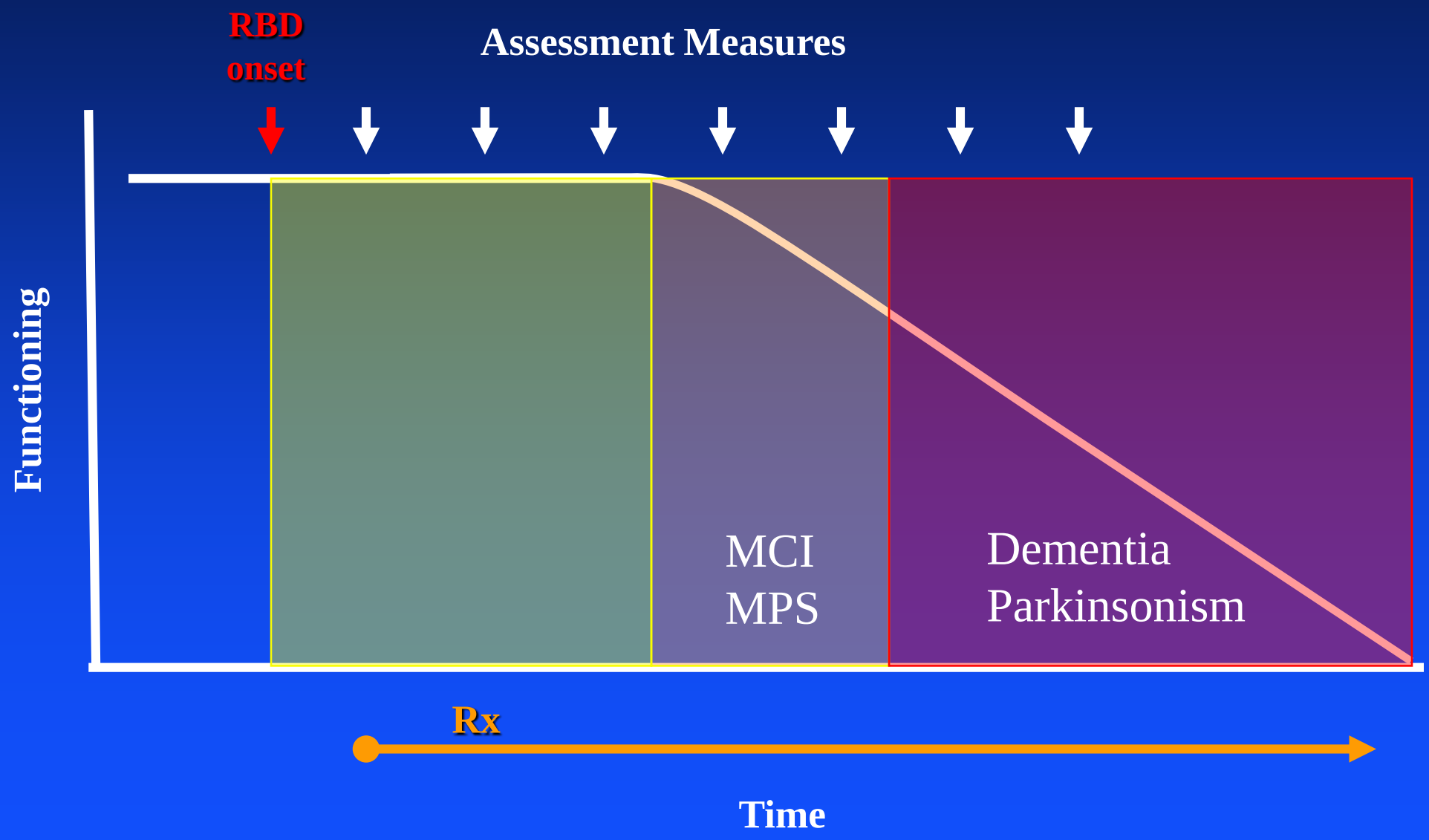
Theoretical Considerations for RBD to MCI to DLB



Planning for Disease-Modifying Therapies in LBD



Planning for Disease-Modifying Therapies in LBD



Planning for Disease-Modifying Therapies in LBD

Immunotherapy for neurodegenerative diseases: Focus on α-synucleinopathies

Elvira Valera, Eliezer Masliah *

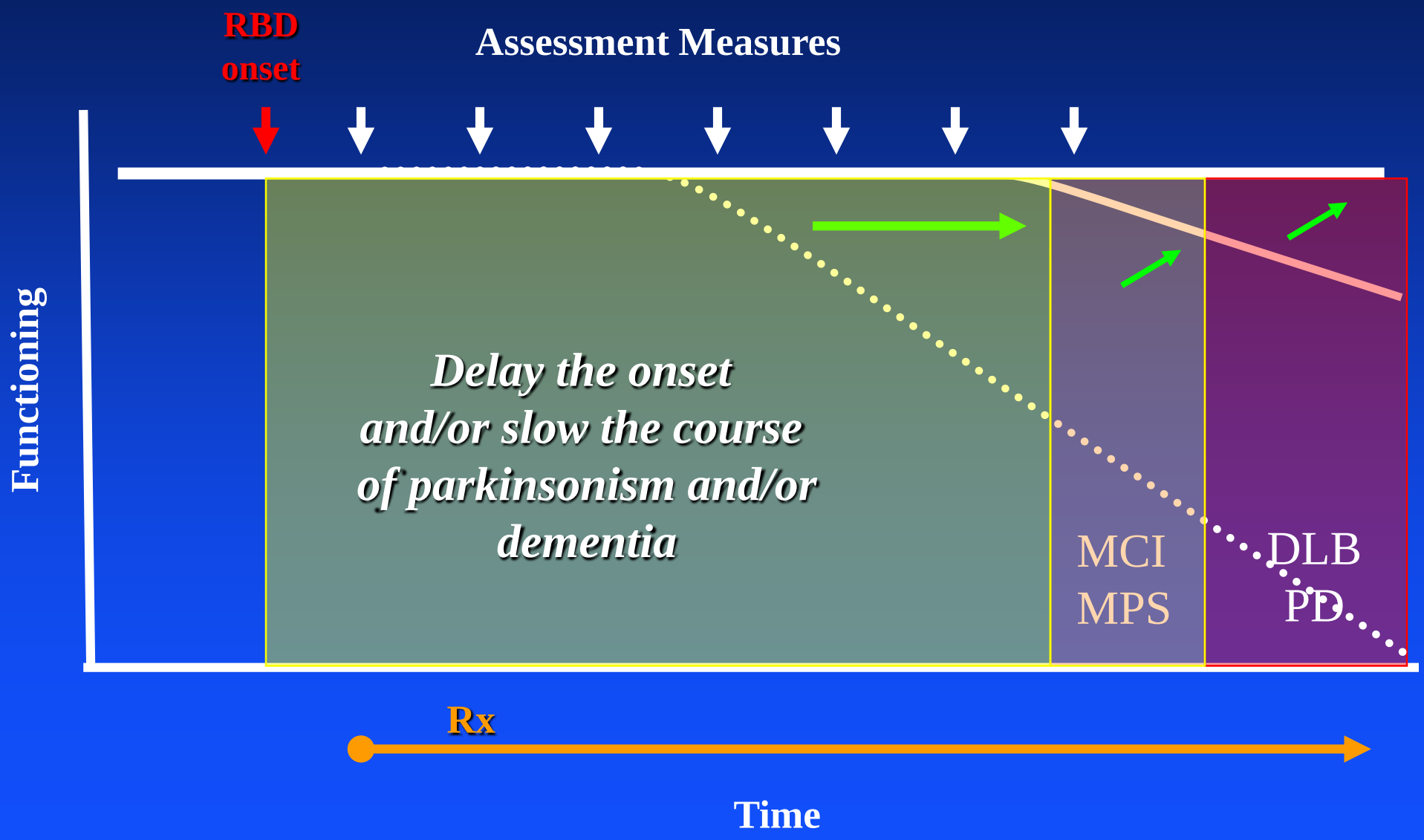
Pharm Ther 2013

α-Synuclein Immunotherapy Blocks Uptake and Templated Propagation of Misfolded α-Synuclein and Neurodegeneration

Hien T. Tran,[1,2] Charlotte Hiu-Yan Chung,[1] Michiyo Iba,[1] Bin Zhang,[1] John Q. Trojanowski,[1] Kelvin C. Luk,[1] and Virginia M.Y. Lee[1,*]

Tran et al, Cell Reports 2014

Planning for Disease-Modifying Therapies in LBD



Future Directions

- Advance our understanding of the pathophysiology of human RBD
  - Which specific nuclei/networks are involved?
  - Are networks involved in REM sleep control selectively vulnerable to neurodegeneration, particularly in the synucleinopathies? If so, why?

Future Directions

- Study the natural history of RBD, RBD+MCI, RBD+MPS to prepare for future disease modifying therapies
  - Identify which iRBD pts have an underlying neurodegenerative disorder
  - Identify which proteinopathy (ie, α-synuclein, tau, etc.) is causing RBD in those with an underlying neurodegenerative disorder
  - Identify which phenotype will evolve, and when
  - Identify those at short-term risk of developing parkinsonism and/or cognitive impairment for treatment trials

Future Directions

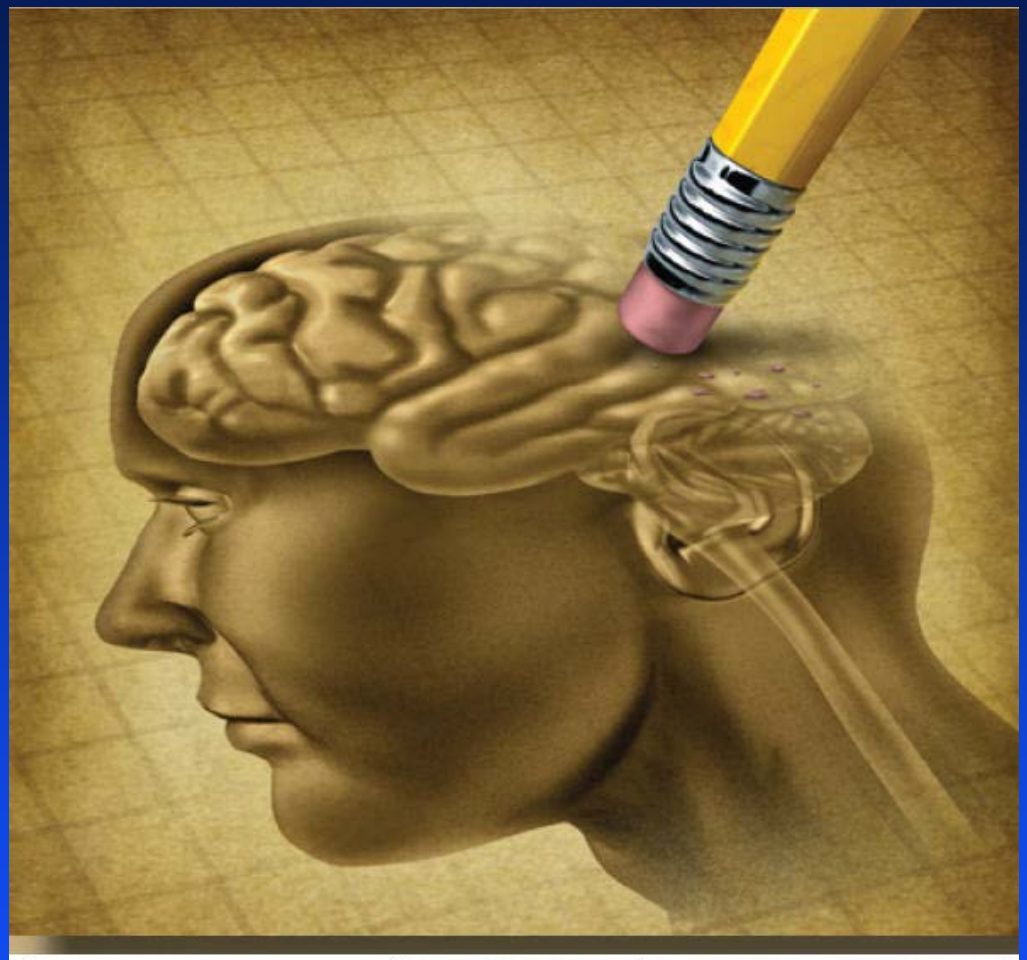
- Support or refute the Braak staging scheme as it relates to RBD, and to the MCI/DLB phenotype

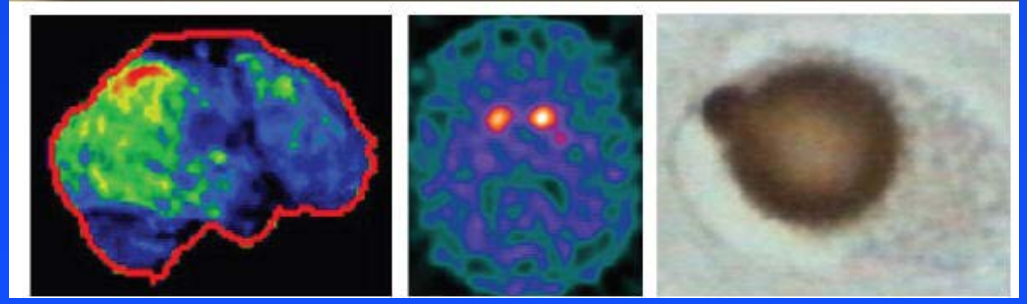
- Screen for RBD to assess epidemiology of the parasomnia, and to detect those who could benefit from eventual therapy

- Characterize “prodromal RBD” by quantifying the degree of RSWA on PSGs for clinical and research purposes; characterize REM behavioral events

- Develop or refine more optimal biomarkers for the synucleinopathies

International Dementia with Lewy Bodies Conference





December 1-4, 2015

Marriott Harbor Beach Resort & Spa

Fort Lauderdale, Florida

Abstract Deadline – June 2015

Diagnosis
Epidemiology
Clinical aspects
Neuropsychology
Neuroimaging
Therapeutics

Genetics
Biofluid markers
Neuropathology
Molecular biology
Animal models
Controversies

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Maja Tippmann-Peikert, MD
Mithri Junna, MD
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Tanis Ferman, PhD
Glenn Smith, PhD
Robert Ivnik, PhD
John Lucas, PhD

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Neill Graff-Radford, MBChB
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Kejal Kantarci, MD
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Val Lowe, MD

Joseph Parisi, MD
Dennis Dickson, MD
Melissa Murray, PhD

Clif Saper, MD, PhD
Heiko Braak, MD
Kelly Del Tredici, MD, PhD
Alon Avidan, MD, MPH
Mark Mahowald, MD
Ron Postuma, MD, MPH
Alex Iranzo, MD
Carlos Schenck, MD
Many others

Departments of Neurology, Psychiatry and Psychology, Diagnostic Radiology, Pathology and Laboratory Medicine, Neuropathology Laboratory, Community Internal Medicine, Health Sciences Research, and Center for Sleep Medicine,
Mayo Clinic Rochester and Mayo Clinic Jacksonvile;
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M.H. Udall PD Center of Excellence Grant, Mayo Foundation

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