

17th Annual Sleep Medicine Virtual Course

Saturday, March 22, 2025



Sleep in Neurodegenerative Disorders

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Conflict of Interest Disclosures for Speakers

Bradley F. Boeve, MD

disclosed relationships with Cognition Therapeutics (grant support to institution for clinical trial), Alector (grant support to institution for clinical trial), and EIP Pharma (grant support to institution for clinical trial).

The relevant financial relationships have been mitigated.

Sleep in Neurodegenerative Disorders

Learning Objectives

Upon completion of this course, attendees should be able to:

- Describe updated concepts and terminology in neurodegenerative syndromes/diseases
- Describe key sleep issues in select neurodegenerative disorders
- Apply a practical approach to managing key sleep issues in neurodegenerative disorders
- Provide resources for fellow clinicians and patients/families

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Sleep in Neurodegenerative Disorders

Concepts and Terminology in Neurodegenerative Disorders

Movement away from conflating terms that reflect a syndrome and disease

Classic Terminology

Syndrome

Alzheimer's disease

Parkinson's disease

Pick's disease

Corticobasal degeneration

Progressive supranuclear palsy

Disease

Alzheimer's disease

Parkinson's disease

Pick's disease

Corticobasal degeneration

Progressive supranuclear palsy

Sleep in Neurodegenerative Disorders

Concepts and Terminology in Neurodegenerative Disorders

Movement away from conflating terms that reflect a syndrome and disease

Current Terminology

Syndrome

Alzheimer's disease dementia (ADem)

Parkinson's disease (PD)

Frontotemporal dementia (FTD)

Corticobasal syndrome (CBS)

Progressive supranuclear palsy – Richardson's syndrome (PSP-RS)

Disease

Alzheimer's disease (AD)

Lewy body disease (LBD) or Neuronal Synuclein Disease (NSD)

Frontotemporal lobar degeneration (FTLD)

Corticobasal degeneration (CBD)

Progressive supranuclear palsy (PSP)

Sleep in Neurodegenerative Disorders

Concepts and Terminology in Neurodegenerative Disorders

The terms and associated underlying neurodegenerative diseases have expanded

Updated Terminology

Syndrome

Mild cognitive impairment (MCI)
Alzheimer's disease dementia (ADem)
Parkinson's disease (PD)
Parkinson's disease with dementia (PDD)
Dementia with Lewy bodies (DLB)
Multiple system atrophy (MSA)
Behavioral variant frontotemporal dementia (bvFTD)
Primary progressive aphasia (PPA)
Corticobasal syndrome (CBS)
Progressive supranuclear palsy – Richardson's syndrome (PSP-RS)
Amyotrophic lateral sclerosis (ALS)
Huntington's disease (HD)

Disease

Alzheimer's disease (AD)
Lewy body disease (LBD) or Neuronal Synuclein Disease (NSD)
Multiple system atrophy (MSA) or Glial Synuclein Disease
Frontotemporal lobar degeneration (FTLD)
Corticobasal degeneration (CBD)
Progressive supranuclear palsy (PSP)
Pick's disease (Pick)
Amyotrophic lateral sclerosis (ALS)
Huntington's disease (HD)

Sleep in Neurodegenerative Disorders

Concepts and Terminology in Neurodegenerative Disorders

The neurodegenerative diseases and associated proteinopathies are better clarified

Disease

Alzheimer's disease (AD) – $A\beta$ and mixed 4R/3R tau

Lewy body disease (LBD) – α -synuclein (esp in neurons)

Multiple system atrophy (MSA) - α -synuclein (esp in glia)

Frontotemporal lobar degeneration (FTLD) – 4R tau, 3R tau, TDP-43, FET

Corticobasal degeneration (CBD) – 4R tau

Progressive supranuclear palsy (PSP) – 4R tau

Pick's disease (Pick) – 3R tau

FTLD-TDP-43

Amyotrophic lateral sclerosis (ALS) – TDP-43

Huntington's disease (HD) - huntingtin

Sleep in Neurodegenerative Disorders

Concepts and Terminology in Neurodegenerative Disorders

A β

4R, 3R, mixed 4R/3R tau

α -synuclein

TDP-43

FET

huntingtin

Proteinopathy

Each proteinopathy involves a protein that misfolds, aggregates into inclusions, and these inclusions and associated pathophysiologic processes affect the normal functioning of the neurons and/or glial, thereby leading to degeneration.

Selective vulnerability

Each misfolded protein has a propensity to affect certain neuronal populations and spare many other populations.

Topographic/spatial heterogeneity

This selective vulnerability affects certain neuronal networks and spares others, thereby leading to different topographic/spatial distributions of degeneration.

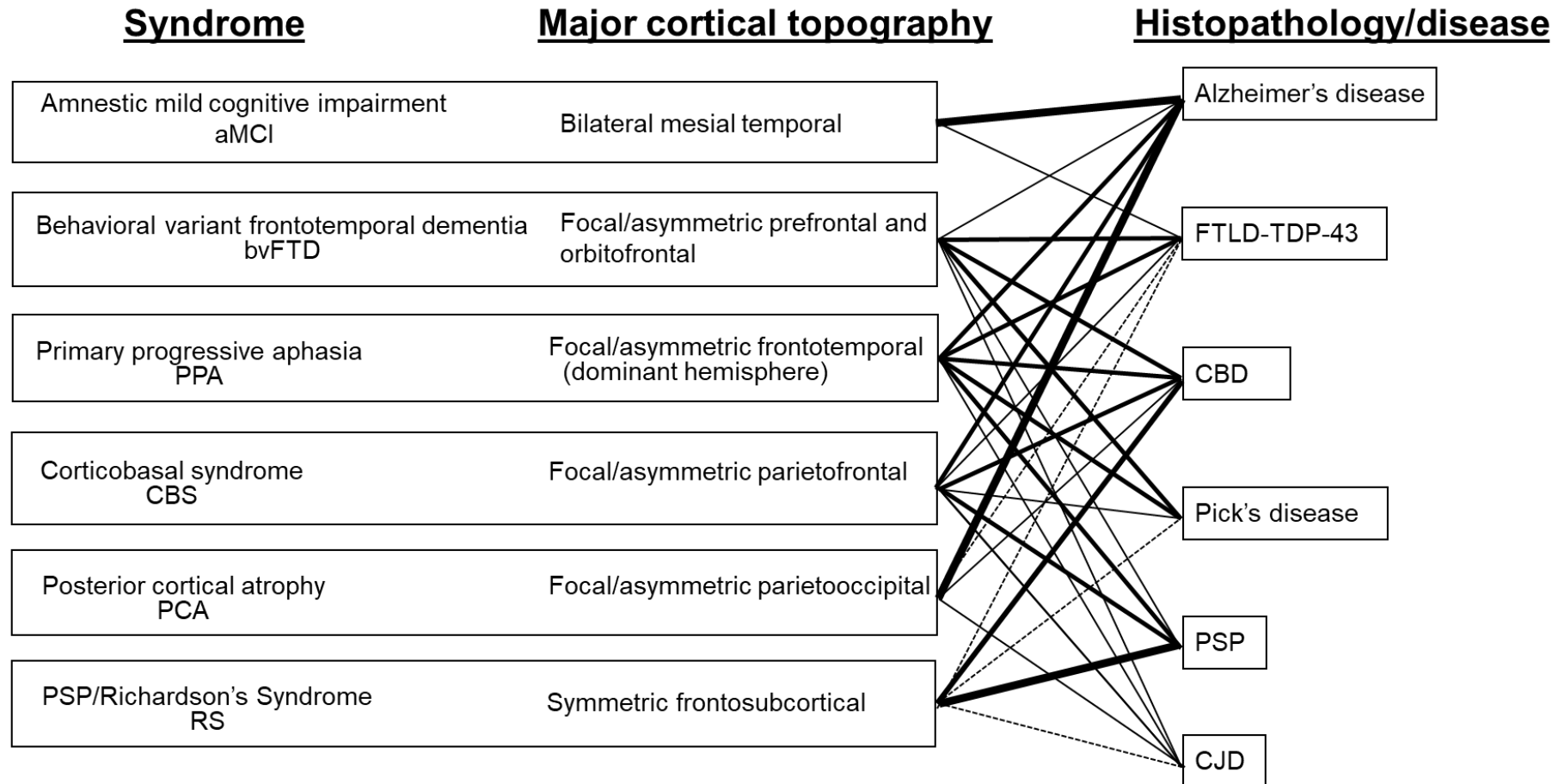
Inter-individual variability

While there are general proteinopathy-neural network tendencies that lead to the same syndrome, there is still considerable inter-individual variability.

Sleep in Neurodegenerative Disorders

Concepts and Terminology in Neurodegenerative Disorders

There is considerable clinicopathologic heterogeneity, underscoring the need for better biofluid and neuroimaging biomarkers.



Sleep in Neurodegenerative Disorders

Concepts and Terminology in Neurodegenerative Disorders

Implications of these complicated concepts in sleep medicine:

- Most sleep data that involves clinically diagnosed patients with 'Alzheimer's disease', 'Parkinson's disease', etc. (ie, without key biomarkers, without pathology) must be interpreted with caution – misdiagnoses occur.
- Much of the sleep data surely includes sizable minorities of patients who do not have the reported disease of interest.
- These issues will surely be clarified as advancements in biomarkers continue to improve, and are used in sleep-neurodegenerative disease analyses.

Sleep in Neurodegenerative Disorders

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Key Sleep Issues in Select Neurodegenerative Disorders

- Alzheimer's disease (AD)
- Lewy body disease (LBD)
 - Parkinson's disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB)
- Multiple system atrophy (MSA)
- Behavioral variant frontotemporal dementia (bvFTD)
- Progressive supranuclear palsy (PSP), including PSP-RS
- Amyotrophic lateral sclerosis (ALS)
- Huntington's disease (HD)

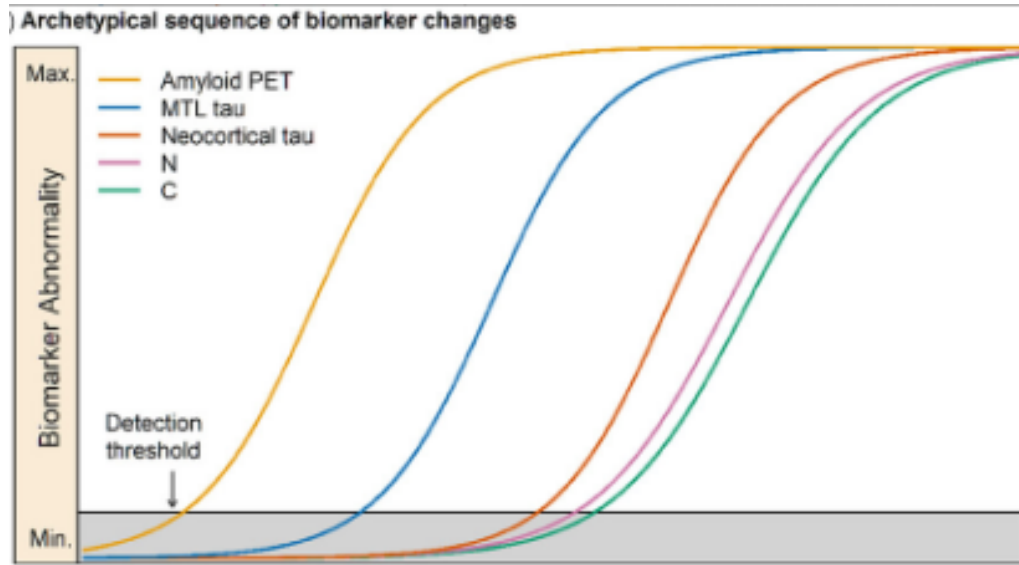
Key Sleep Issues in Select Neurodegenerative Disorders

Alzheimer's Disease Dementia/Alzheimer's Disease

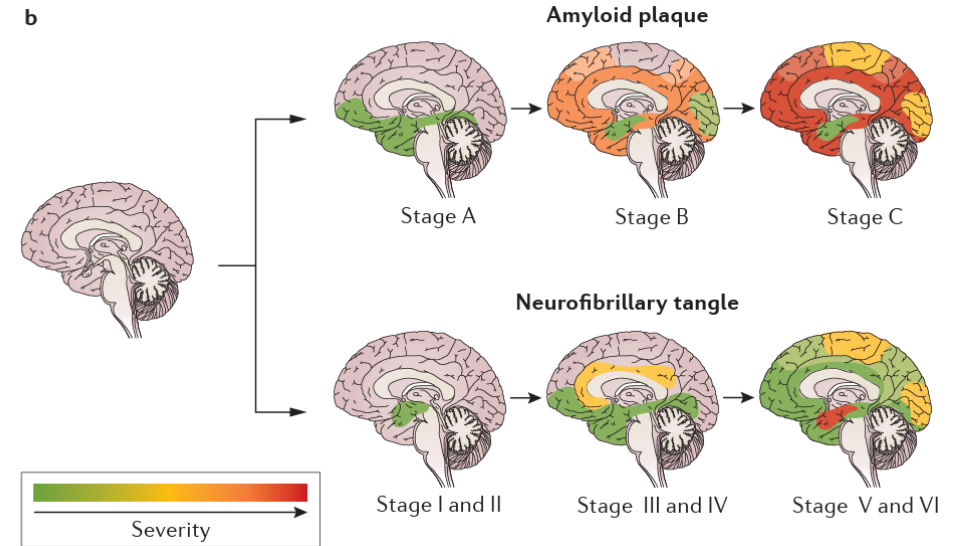
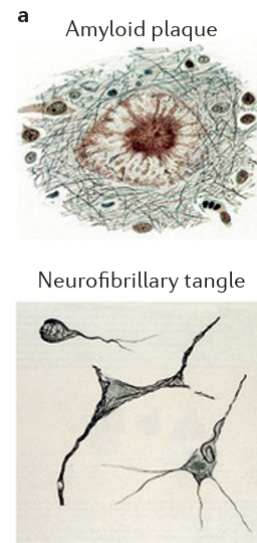
- AD pathoanatomy
- AD and OSA associations
- Effects of treatment for sleep disorders in AD/ADem

Key Sleep Issues in Select Neurodegenerative Disorders

Alzheimer's Disease – Pathophysiology/Pathoanatomy



Jack et al, Alz Dem 2024



Masters et al, Nature Reviews 2015

Key Sleep Issues in Select Neurodegenerative Disorders

OSA and AD – Bidirectional Relationship

Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease

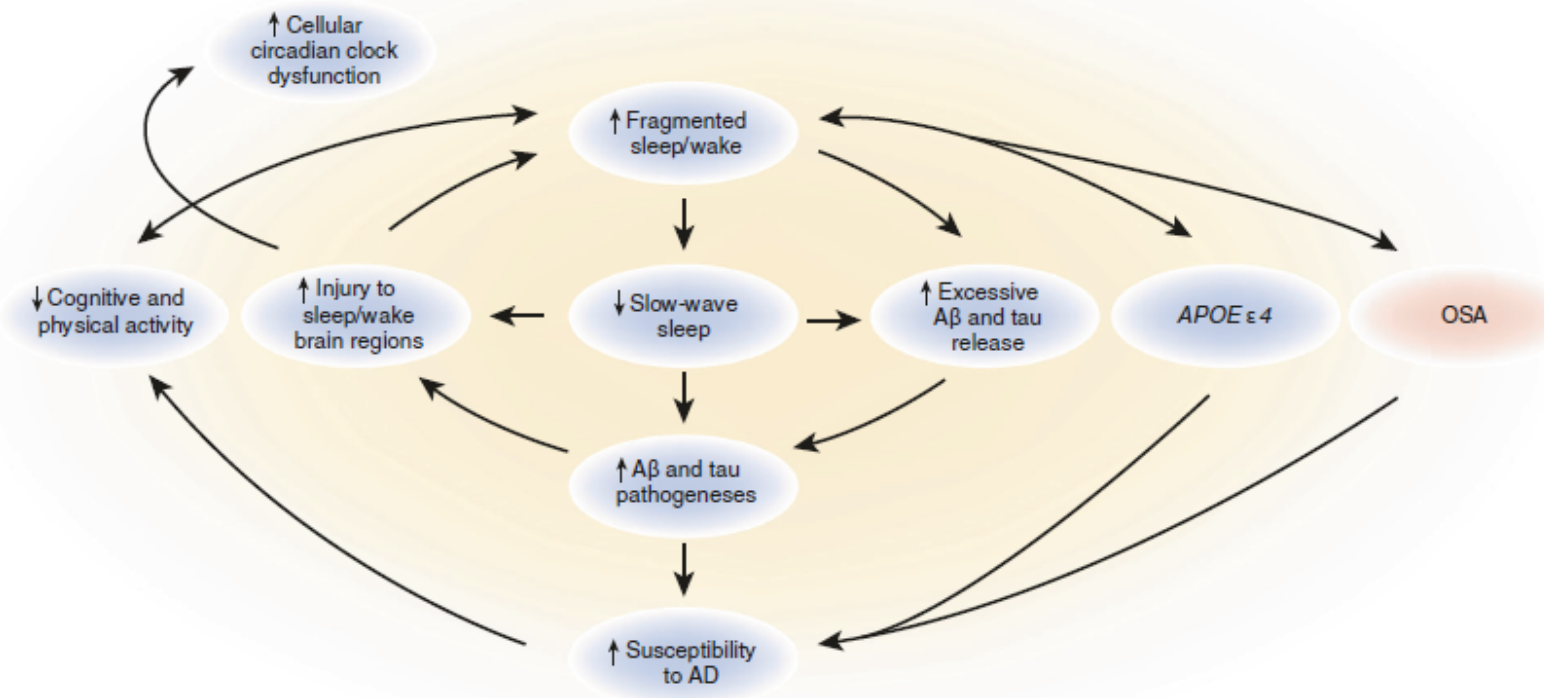
Brendan P. Lucey^{1,2*}, Austin McCullough³, Eric C. Landsness¹, Cristina D. Toedebusch¹, Jennifer S. McLeland¹, Aiad M. Zaza³, Anne M. Fagan^{1,2,4}, Lena McCue⁵, Chengjie Xiong⁵, John C. Morris^{1,2,4}, Tammie L. S. Benzinger^{3,4}, David M. Holtzman^{1,2,4*}

Sci Transl Med 2019

Slow wave sleep disruption increases cerebrospinal fluid amyloid- β levels

Yo-El S. Ju,^{1,2,*} Sharon J. Ooms,^{3,4,5,*} Courtney Sutphen,^{1,2} Shannon L. Macauley,^{1,2} Margaret A. Zangrilli,¹ Gina Jerome,^{1,2} Anne M. Fagan,^{1,2,6} Emmanuel Mignot,⁷ John M. Zempel,¹ Jurgen A.H.R. Claassen^{3,4,5} and David M. Holtzman^{1,2,6}

Brain 2017



Ju et al, Nat Rev Neurol 2014; Lucey et al, Ann Neurol 2018; Wang and Holtzman, Neuropsychopharm 2020

Key Sleep Issues in Select Neurodegenerative Disorders

Select Examples: Therapeutic Effects on Sleep and AD

A Multicenter, Placebo-controlled Trial of Melatonin for Sleep Disturbance in Alzheimer's Disease

Clifford Singer, MD¹; Rochelle E. Tractenberg, PhD, MPH²; Jeffrey Kaye, MD¹; Kim Schafer, MS³; Anthony Gamst, PhD³; Michael Grundman, MD, MPH³; Ronald Thomas, PhD³; Leon J. Thal, MD³ for the Alzheimer's Disease Cooperative Study



SLEEP 2003

¹⁸F-FDG PET, cognitive functioning, and CSF biomarkers in patients with obstructive sleep apnoea before and after continuous positive airway pressure treatment

Mariana Fernandes¹ · Luisa Mari² · Agostino Chiaravalloti^{3,4} · Barbara Paoli¹ · Marzia Nuccetelli⁵ · Francesca Izzi² · Maria Pia Giambrone² · Riccardo Camedda³ · Sergio Bernardini⁵ · Orazio Schillaci^{3,4} · Nicola Biagio Mercuri^{2,6} · Fabio Placidi^{1,2} · Claudio Liguori^{1,2}

J Neurol 2022

Suvorexant Acutely Decreases Tau Phosphorylation and A β in the Human CNS

Brendan P. Lucey, MD, MSCI ^{1,2,3} Haiyan Liu, MD,¹ Cristina D. Toedebusch, BS,¹ David Freund,¹ Tiara Redrick, MS,¹ Samir L. Chahin, MS,^{1,2} Kwasi G. Mawuenyega, PhD,⁴ James G. Bollinger, PhD,^{1,2} Vitaliy Ovod, MS ^{1,2} Nicolas R. Barthélemy, PhD,^{1,2} and Randall J. Bateman, MD^{1,2}

Ann Neurol 2023

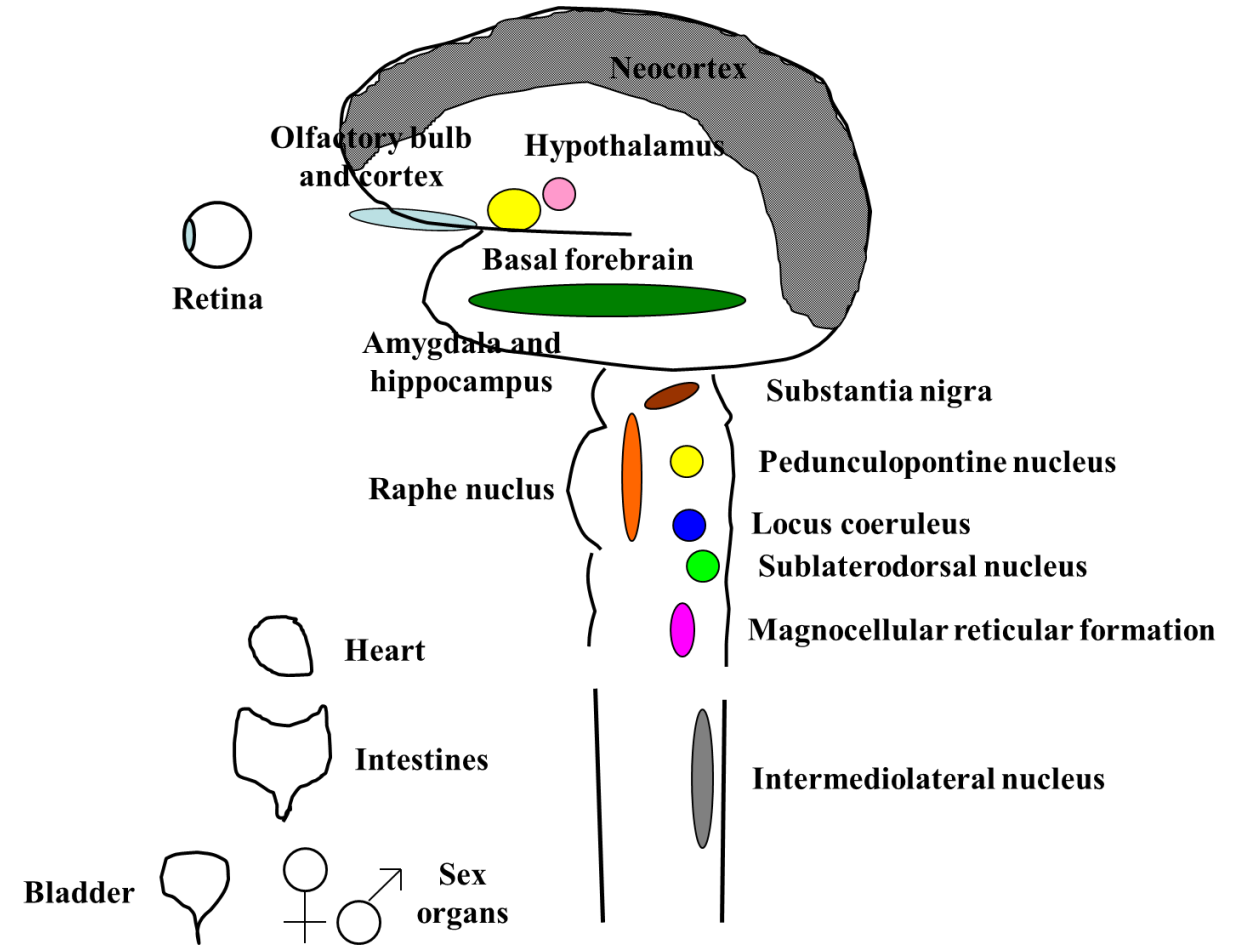
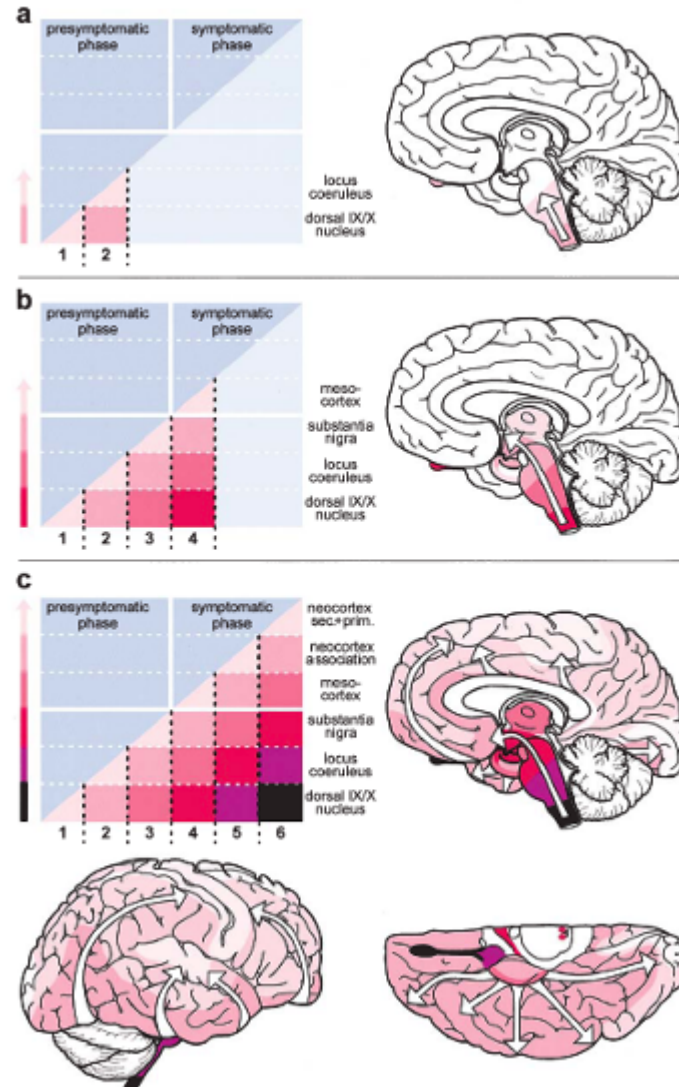
Key Sleep Issues in Select Neurodegenerative Disorders

Lewy Body Disease/Parkinson's Disease and Dementia with Lewy Bodies

- LBD pathoanatomy
- Clinical and imaging features of PD and DLB
- REM sleep behavior disorder and PD/DLB
- OSA and PD

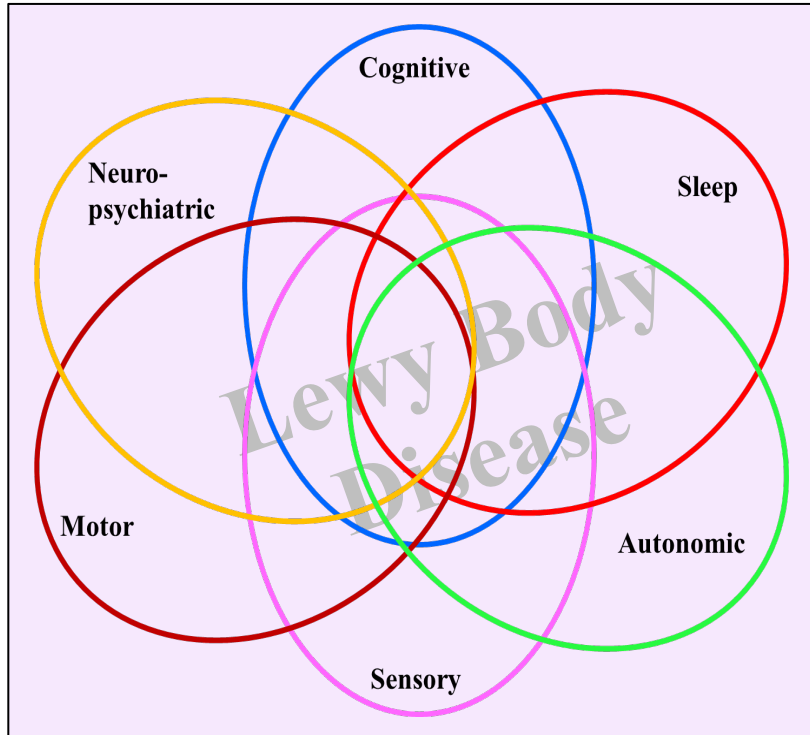
Key Sleep Issues in Select Neurodegenerative Disorders

LBD Pathoanatomy



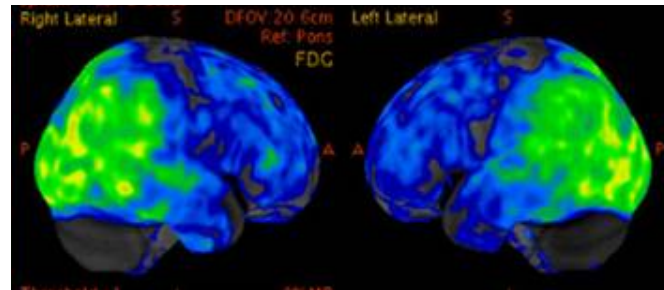
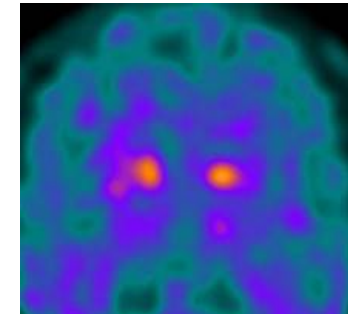
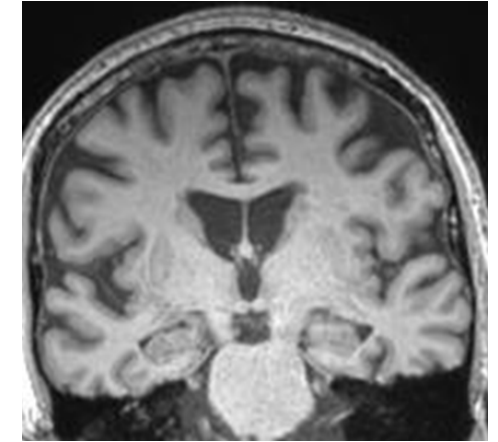
Key Sleep Issues in Select Neurodegenerative Disorders

Clinical and Imaging Features of LBD



Core Clinical Features of DLB

- Parkinsonism
- Visual hallucinations
- Fluctuations
- REM sleep behavior disorder



Key Sleep Issues in Select Neurodegenerative Disorders

Sleep Issues in Dementia with Lewy Bodies

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

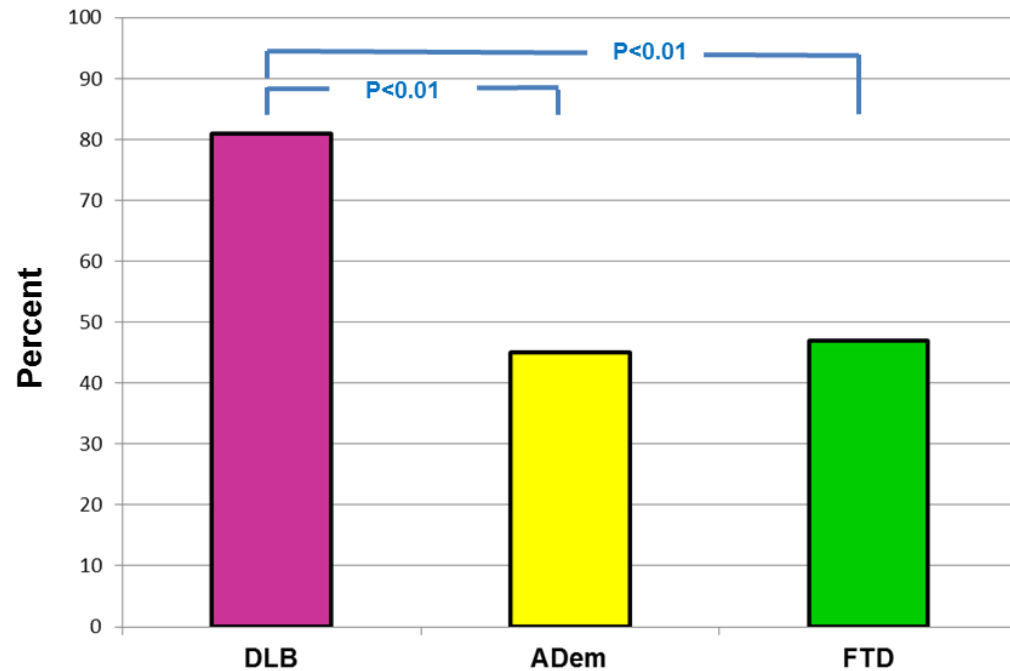
Main points

- AFNARs are very common
 - 76% had >5 arousals/hr
- Sleep efficiency is poor
 - 72% had <80%
 - 49% had <70%
- RBD is common (83%)
- OSA also common (60%)
- PLM arousals are common
 - 45% had >5 arousals/hr

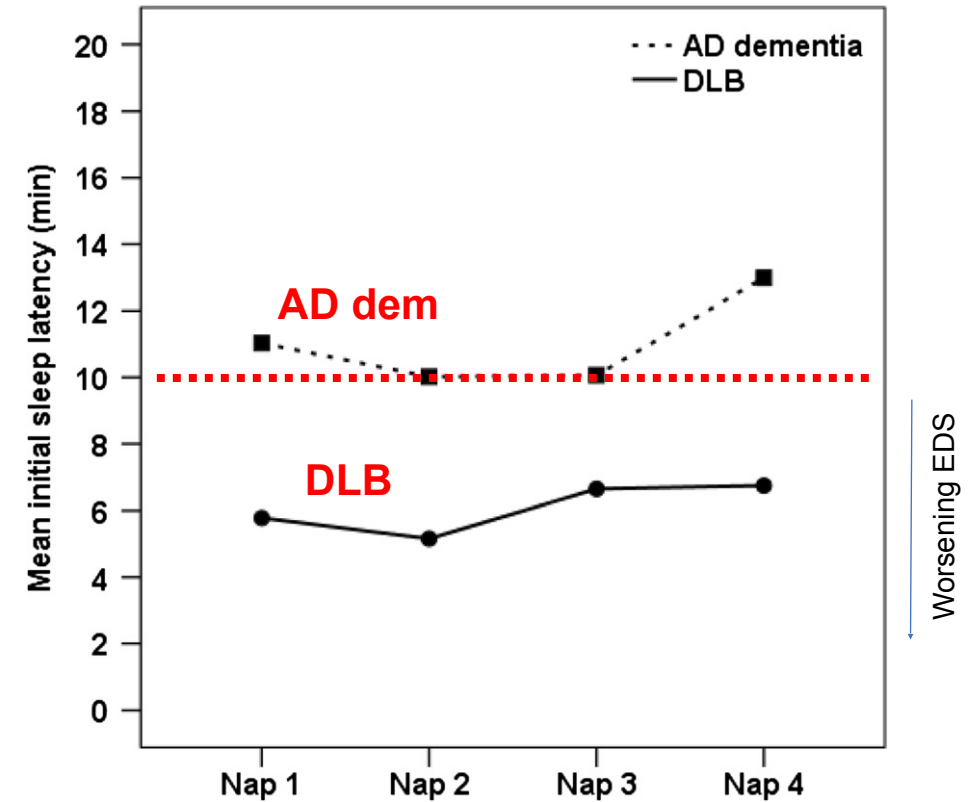
Key Sleep Issues in Select Neurodegenerative Disorders

Sleep Issues in Dementia with Lewy Bodies

ESS Scores ≥ 10 in DLB, ADem and FTD



Boeve et al, Amer J Alz Dis Other Disord 2019



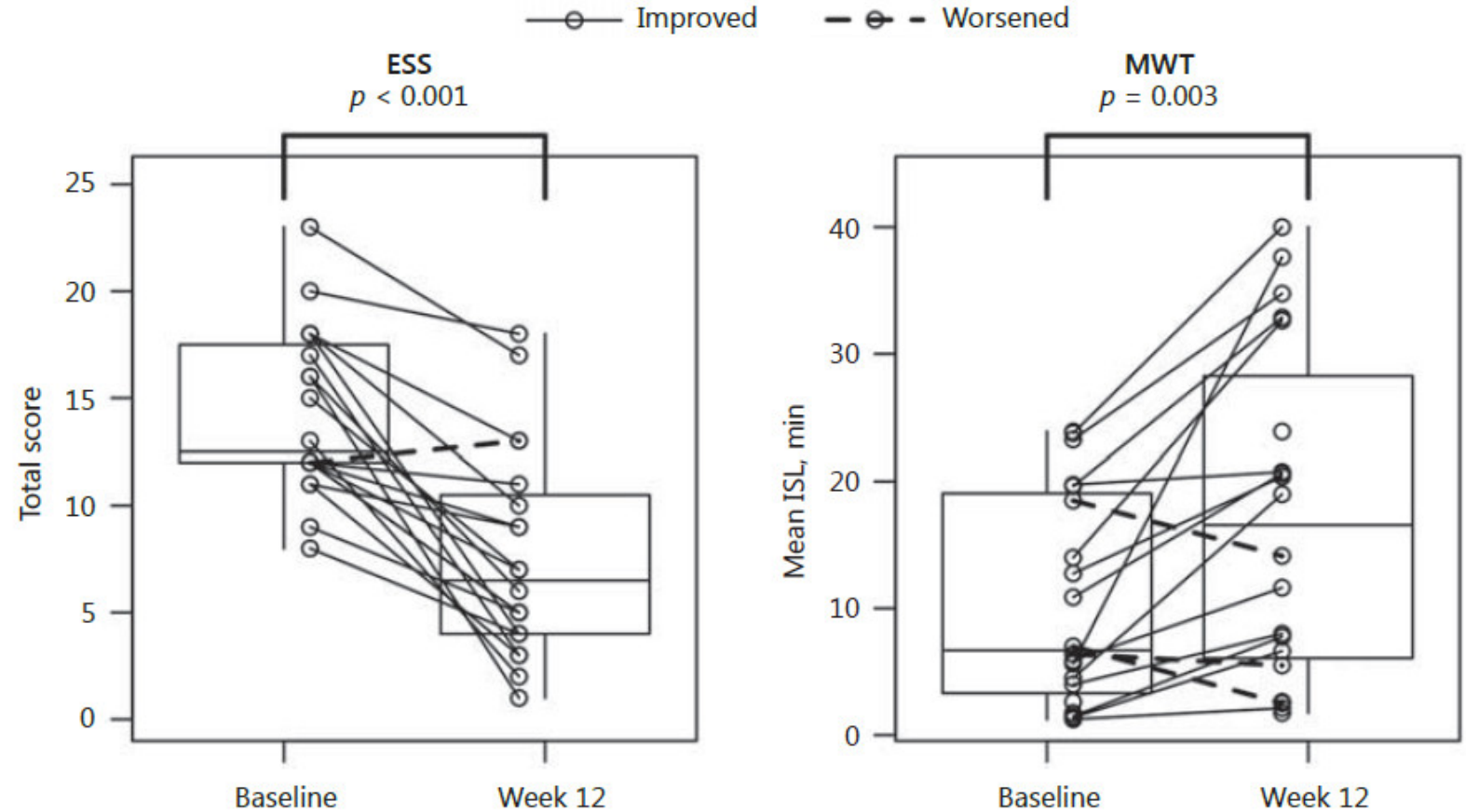
Ferman et al, Alz Res Therapy 2014

Key Sleep Issues in Select Neurodegenerative Disorders

Treatment of EDS in DLB – Pilot Trial with Armodafinil

Efficacy, Safety, and Tolerability of Armodafinil Therapy for Hypersomnia Associated with Dementia with Lewy Bodies: A Pilot Study

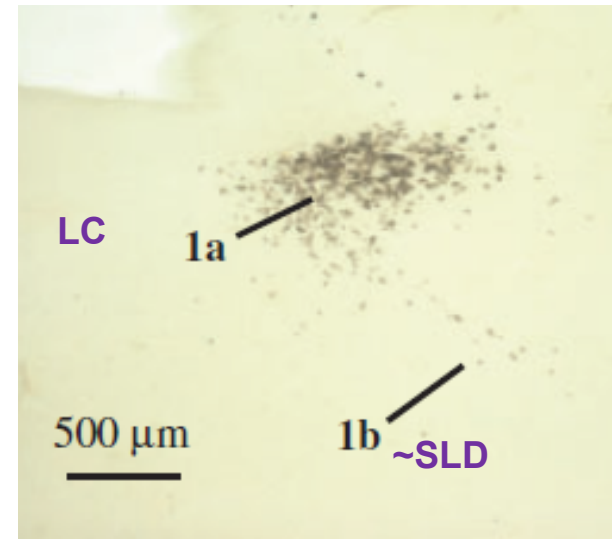
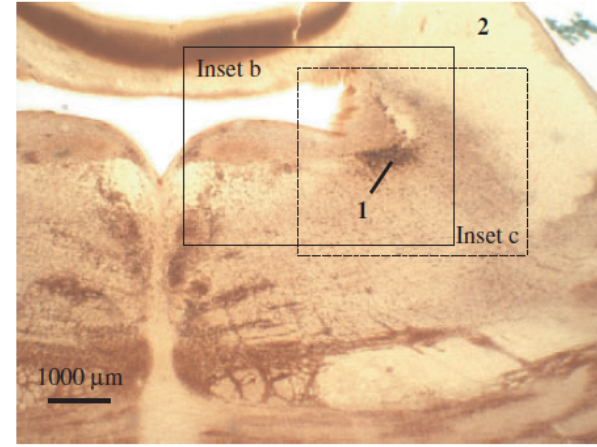
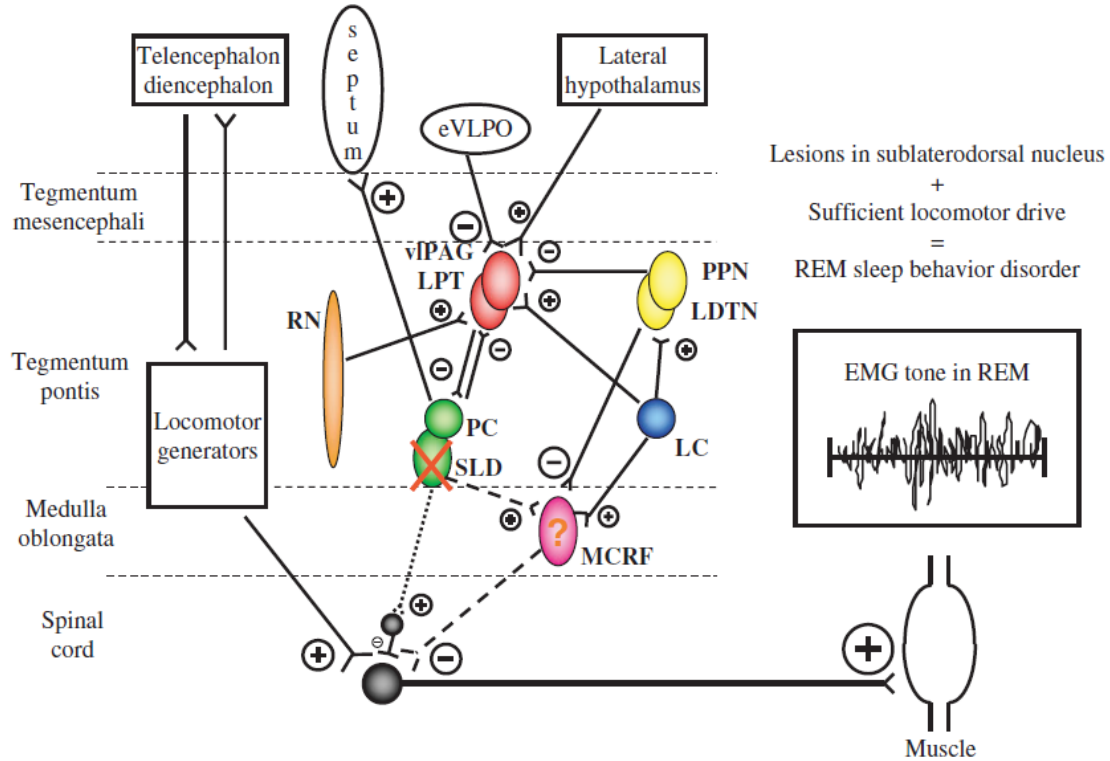
Maria I. Lapid^a Karen M. Kuntz^b Sara S. Mason^b Jeremiah A. Aakre^c
Emily S. Lundt^c Walter Kremers^c Laura A. Allen^b Daniel A. Drubach^b
Bradley F. Boeve^b



Key Sleep Issues in Select Neurodegenerative Disorders

RBD and LBD

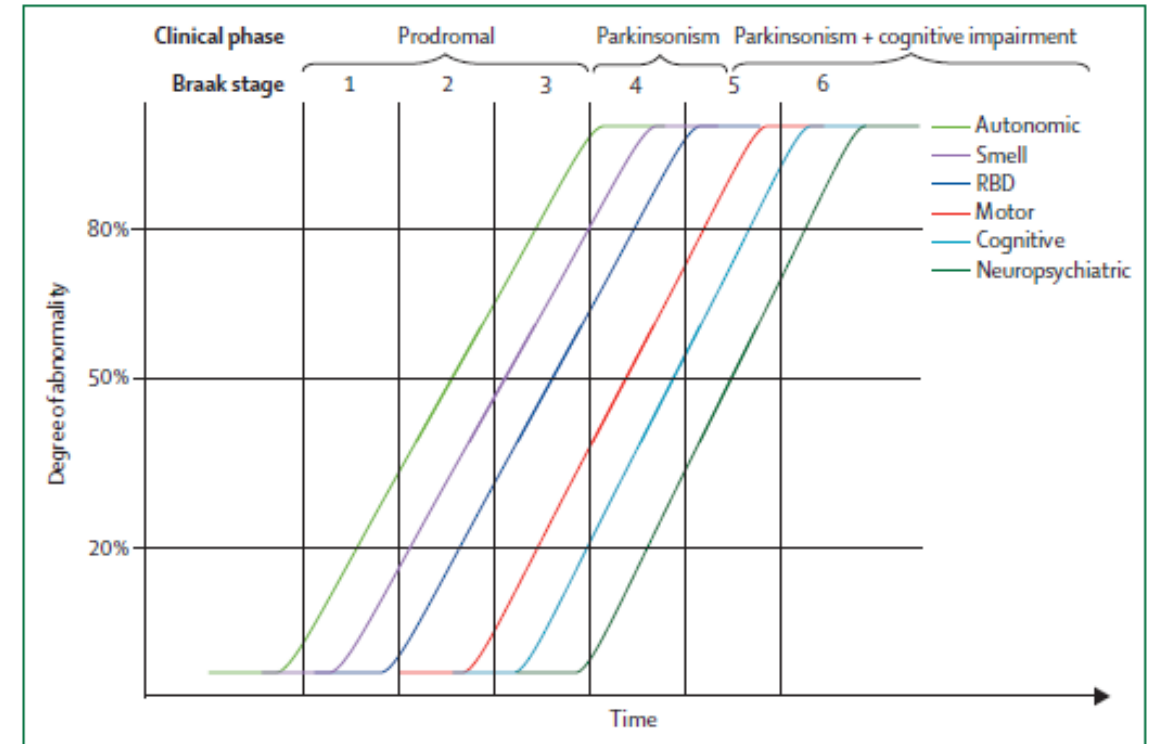
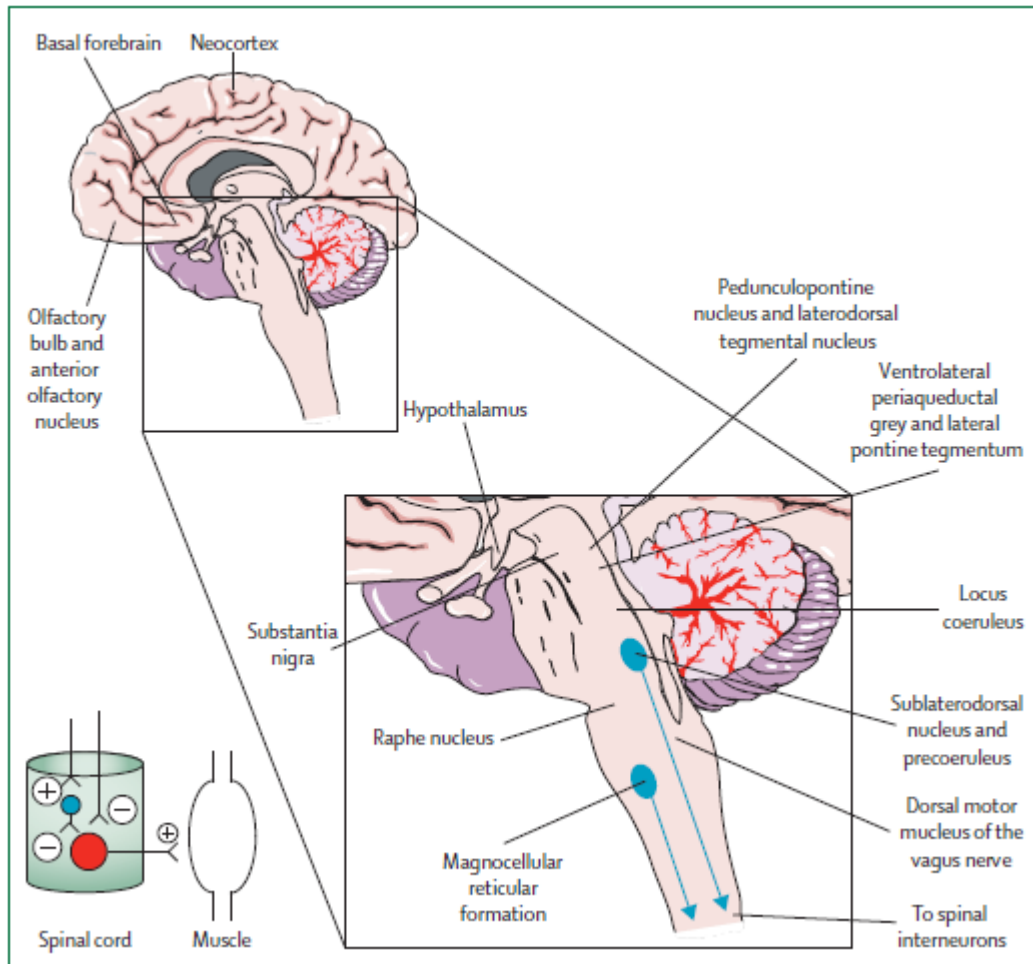
Proposed pathophysiology of REM sleep behavior disorder in humans



Key Sleep Issues in Select Neurodegenerative Disorders

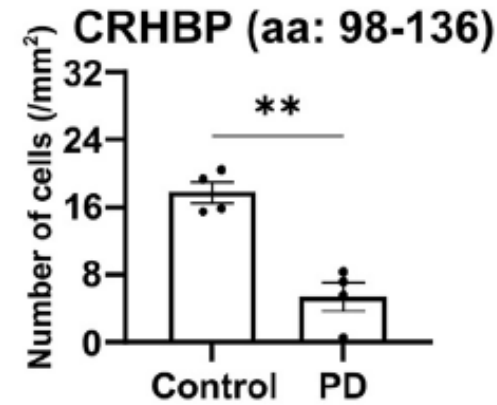
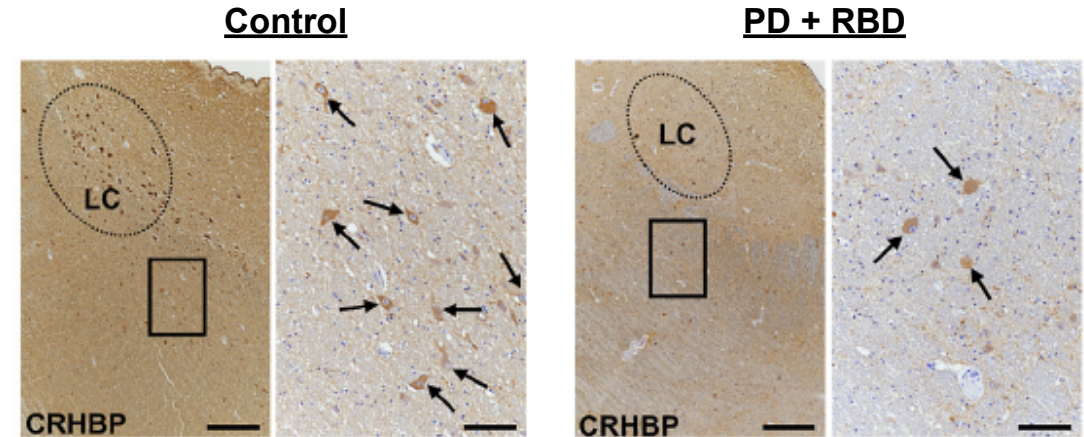
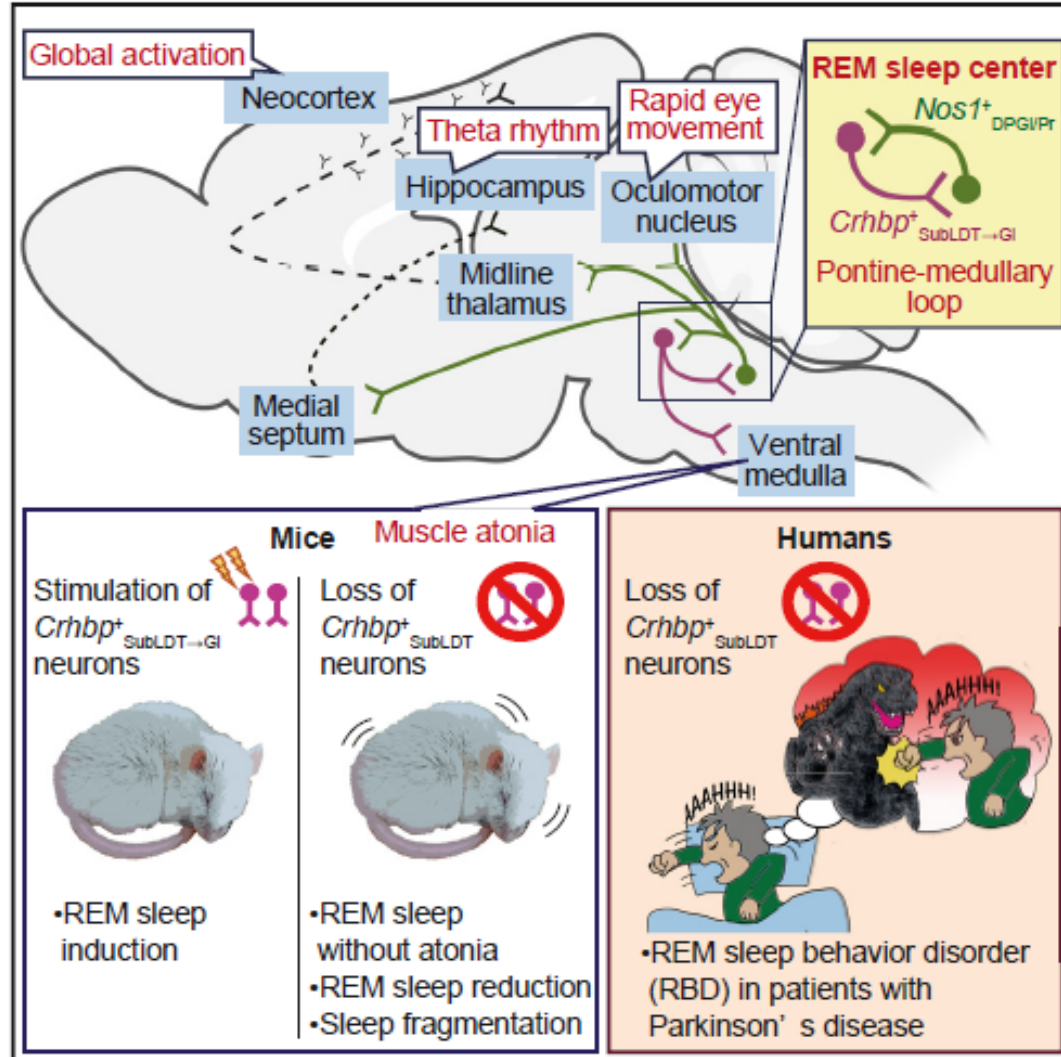
RBD in Parkinson's Disease

Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease



Key Sleep Issues in Select Neurodegenerative Disorders

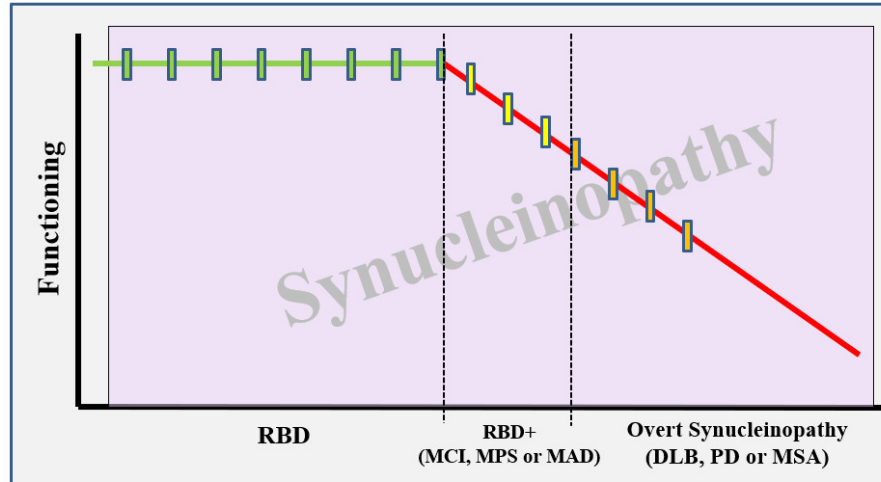
RBD and PD/LBD



Reduced number of corticotropin-releasing hormone-binding protein (CRHBP) neurons in SLD nucleus

Key Sleep Issues in Select Neurodegenerative Disorders

Prospective Characterization of iRBD

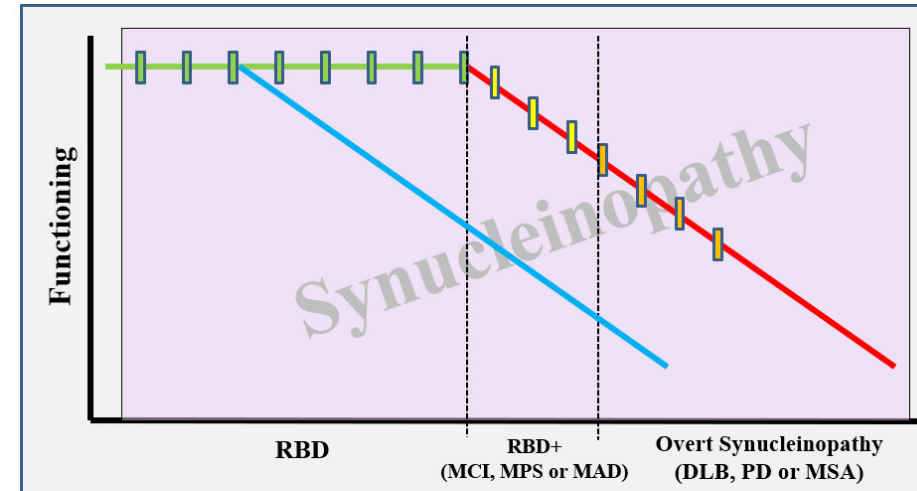
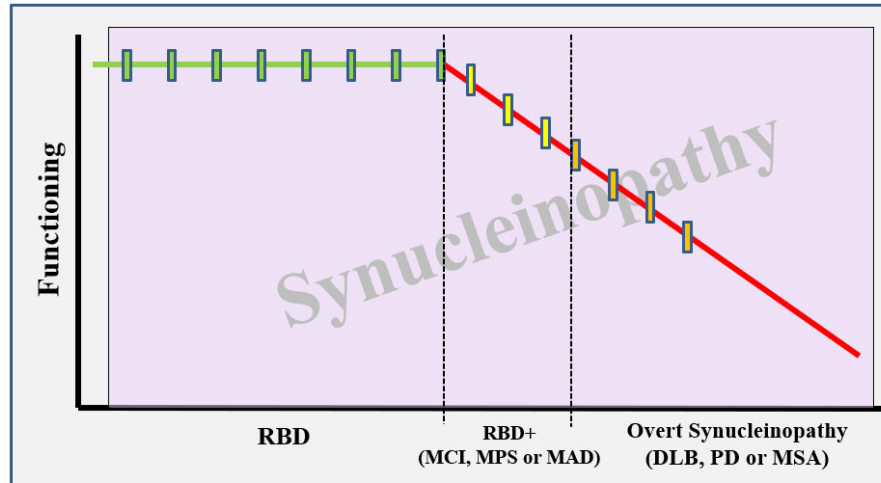


— clinical
— biomarker

□ Comprehensive Battery
(neurologic evaluation, neuropsychological tests, blood sample, MRI scan, DaTscan, CSF sample)

Key Sleep Issues in Select Neurodegenerative Disorders

Prospective Characterization of iRBD

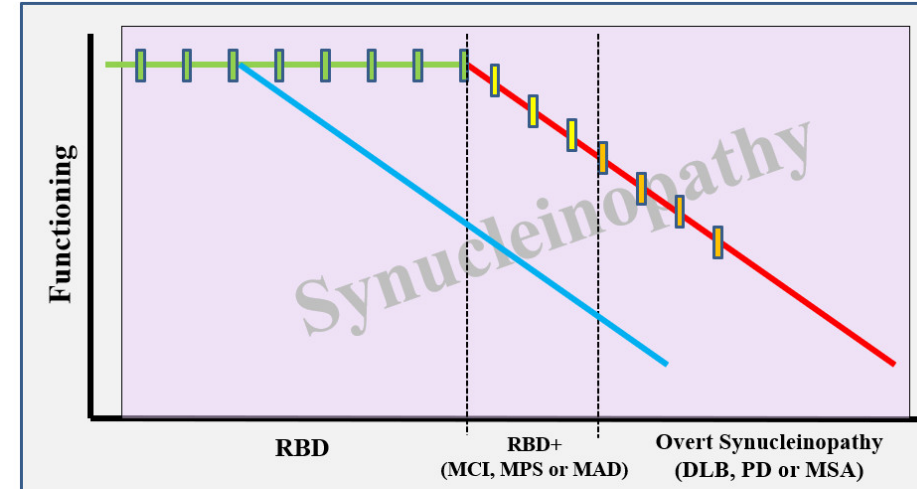
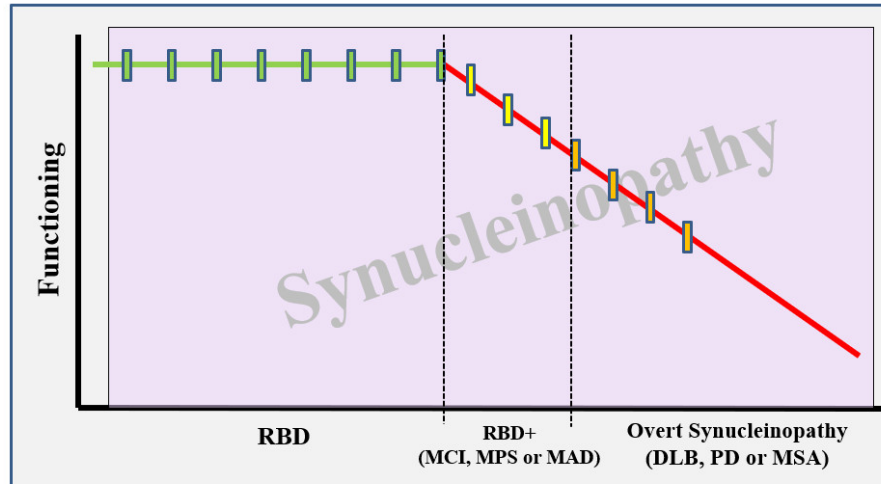


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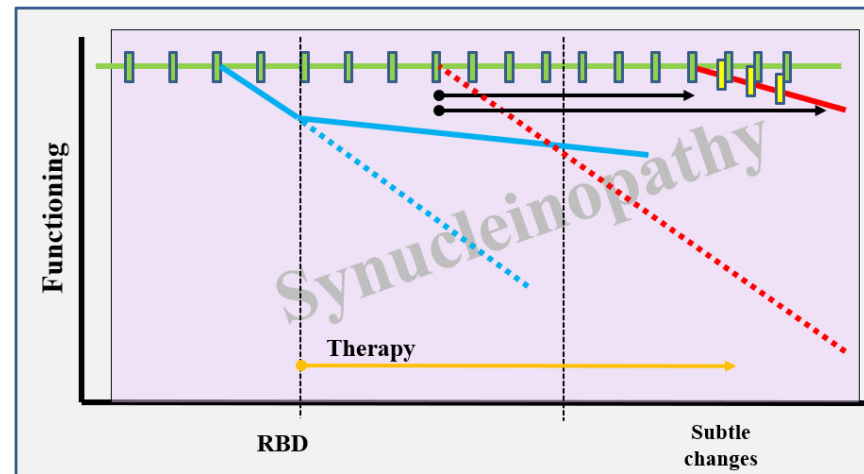
Key Sleep Issues in Select Neurodegenerative Disorders

Prospective Characterization of iRBD



— clinical
— biomarker

Comprehensive Battery
(neurologic evaluation, neuropsychological tests, blood sample, MRI scan, DaTScan, CSF sample)



Parkinson's
Progression
Markers
Initiative

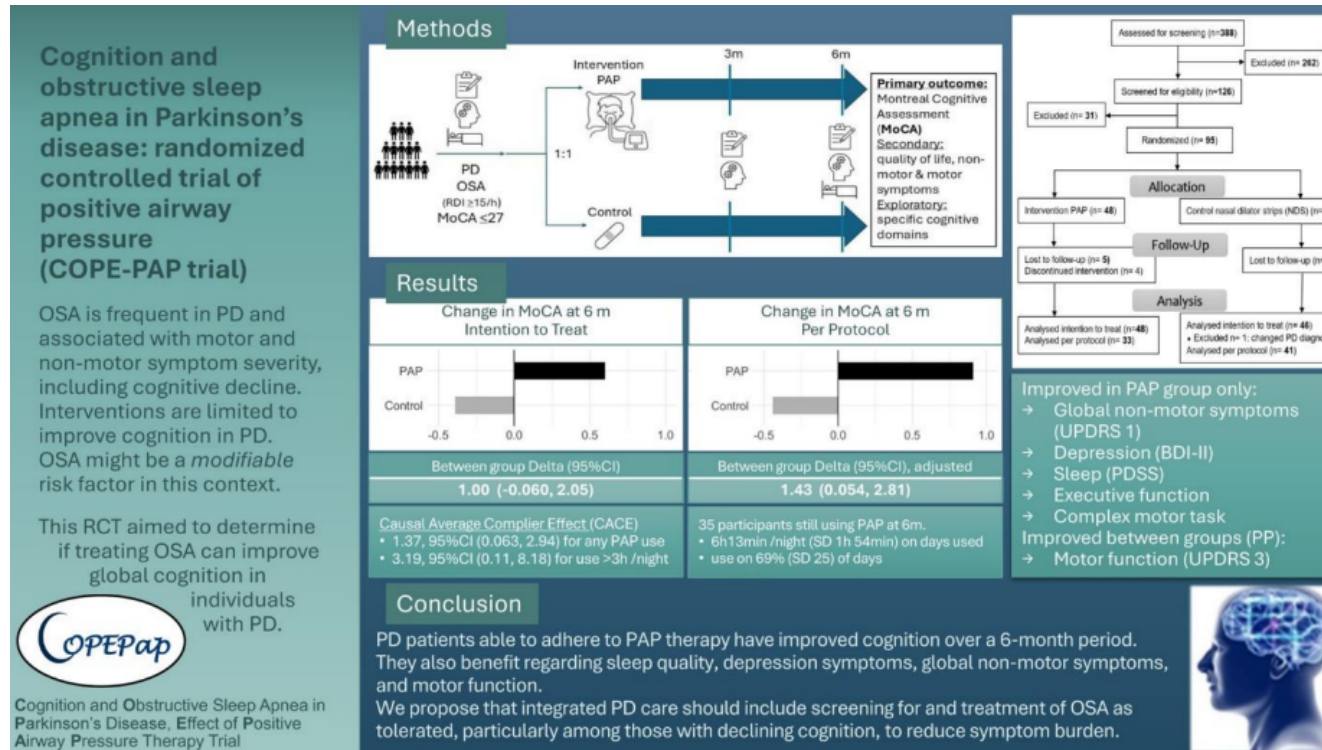
Key Sleep Issues in Select Neurodegenerative Disorders

OSA and PD

Obstructive sleep apnea, CPAP therapy and Parkinson's disease motor function: A longitudinal study

Lingrui Meng^{a,*}, Andrea Benedetti^{a,b}, Anne-Louise Lafontaine^d, Victoria Mery^c, Ann Ross Robinson^e, John Kimoff^{b,e}, Priti Gros^f, Marta Kaminska^{b,e}

Park Rel Disord 2020



Lajoie et al, SLEEP 2025

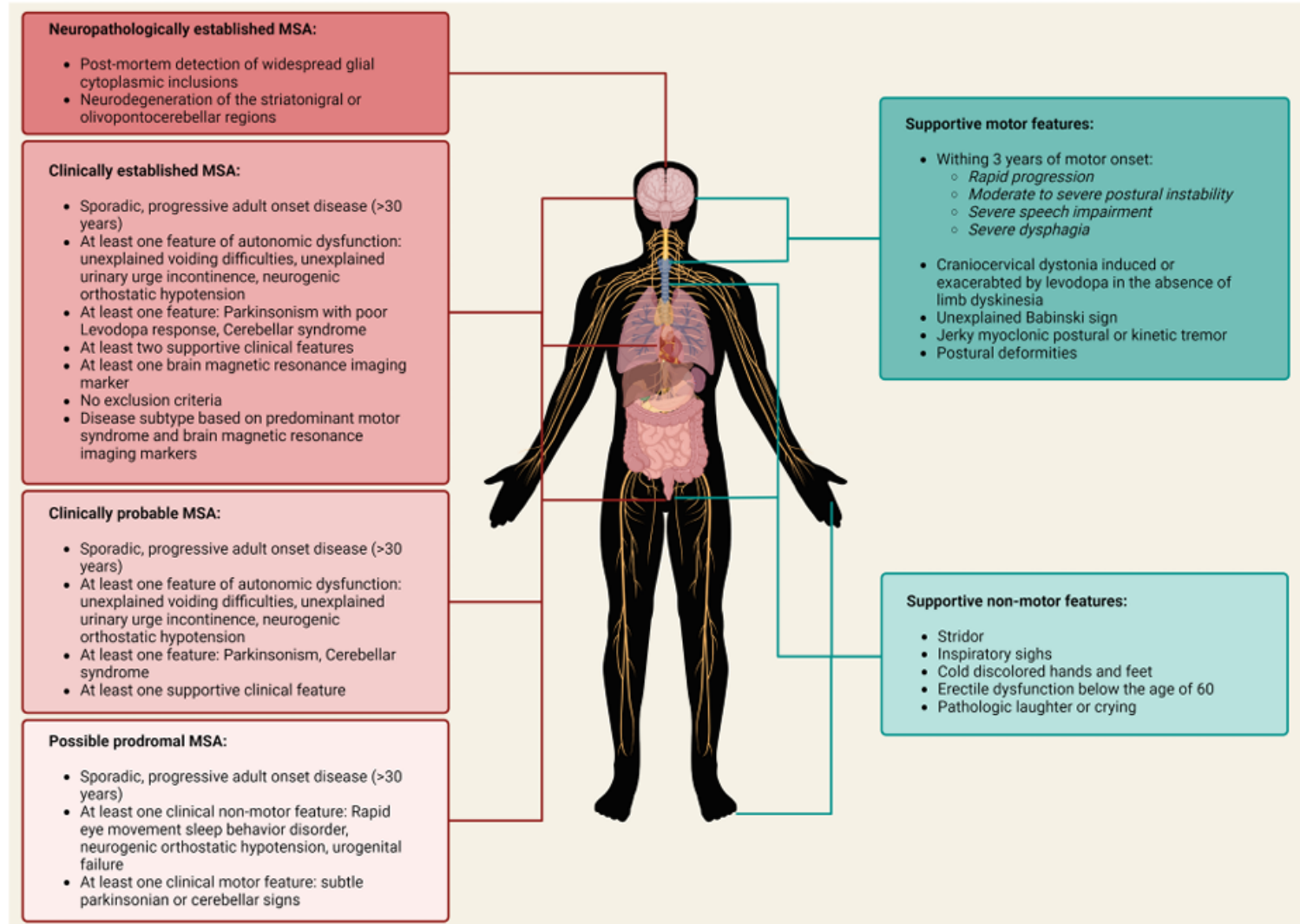
Key Sleep Issues in Select Neurodegenerative Disorders

Multiple System Atrophy

- MSA pathoanatomy and clinical features
- REM sleep behavior disorder
- Nocturnal stridor

Key Sleep Issues in Select Neurodegenerative Disorders

MSA – Pathoanatomy and Clinical Features



Key Sleep Issues in Select Neurodegenerative Disorders

Sleep Issues in Pathology-Proven MSA

Clinical features of autopsy-confirmed multiple system atrophy in the Mayo Clinic Florida brain bank

Shunsuke Koga^a, William P. Cheshire^b, Philip W. Tipton^c, Erika D. Driver-Dunckley^d, Zbigniew K. Wszolek^b, Ryan J. Uitti^b, Neill R. Graff-Radford^b, Jay A. van Gerpen^{b,d}, Dennis W. Dickson^{a,*}

Clinical features in MSA.

	Overall N = 171
RBD	48% (82)
Stridor	18% (31)
Obstructive sleep apnea	28% (48)
Cognitive impairment	35% (60)
Pseudobulbar affect	15% (25)
Hyposmia/ anosmia	12% (21)
Visual hallucinations	11% (19)

Key Sleep Issues in Select Neurodegenerative Disorders

Sleep Issues in MSA

Sleep disturbances in probable multiple system atrophy

Malligurki Raghurama Rukmani^a, Ravi Yadav^{b,*}, Binukumar Bhaskarapillai^c,
Pramod Kumar Pal^b, Talakad Narasappa Sathyaprabha^a

Sleep Med 2024

Sleep disturbance is associated with worsening quality of life in patients with multiple system atrophy

Masakazu Ozawa^{a,b,*}, Hidetomo Murakami^{a,c}, Tomotaka Shiraishi^{a,b},
Hiromasa Matsuno^{a,b}, Keiko Bono^{a,b}, Tadashi Umehara^a, Shusaku Omoto^a,
Renpei Sengoku^a, Hideyuki Shimizu^a, Hiroki Sarukawa^a, Motohiro Okumura^a,
Marina Masui^a, Hiroyuki Kida^a, Haruhiko Motegi^a, Teppei Komatsu^{a,b}, Kenichi Sakuta^a,
Kenichiro Sakai^a, Hidetaka Mitsumura^a, Hirotaka James Okano^b, Yasuyuki Iguchi^a

Clin Neurol Neurosurg 2025

Prevalence and impact of rapid eye movement sleep behavior disorder in multiple system atrophy: a systematic review and meta-analysis

Hui Wang*, Ting Zhang and Wenhui Fan*

Prevalence: Approx 80%

Front Neurol 2024

Key Sleep Issues in Select Neurodegenerative Disorders

Stridor in MSA

Stridor in multiple system atrophy

Consensus statement on diagnosis, prognosis, and treatment

Pietro Cortelli, MD, PhD,* Giovanna Calandra-Buonaura, MD, PhD,* Eduardo E. Benarroch, MD, Giulia Giannini, MD, Alex Iranzo, MD, Phillip A. Low, MD, Paolo Martinelli, MD, Federica Provini, MD, PhD, Niall Quinn, MD, Eduardo Tolosa, MD, PhD, Gregor K. Wenning, MD, PhD, Giovanni Abbruzzese, MD, Pamela Bower, Enrico Alfonsi, MD, Imad Ghorayeb, MD, PhD, Tetsutaro Ozawa, MD, PhD, Claudio Pacchetti, MD, Nicolò Gabriele Pozzi, MD, Claudio Vicini, MD, Angelo Antonini, MD, PhD, Kailash P. Bhatia, MD, Jacopo Bonavita, MD, Horacio Kaufmann, MD, Maria Teresa Pellecchia, MD, PhD, Nicole Pizzorni, MSc, Antonio Schindler, MD, François Tison, MD, PhD, Luca Vignatelli, MD, PhD, and Wassilios G. Meissner, MD, PhD

Conclusion on diagnostic criteria for stridor and definition of stridor in MSA

- Stridor in MSA is a strained, high-pitched, harsh respiratory sound, mainly inspiratory, caused by laryngeal dysfunction leading to narrowing of the rima glottidis. It may occur only during sleep or it may be present both during sleep and wakefulness.
- Stridor may be recognized clinically if present at the time of neurologic examination, with the help of a witness, or by listening to an audio recording.
- Laryngoscopy is suggested to exclude mechanical lesions (e.g., masses and scars) or functional vocal cord abnormalities related to different neurologic conditions (central or peripheral disorders).

Treatment for symptomatic control of stridor

Statements are based on core literature consisting of Class III/IV level studies^{8,10-14,27,29,32,33,35,39,49,51,52} and expert opinion.

- Ventilation during sleep (CPAP) can be useful in the symptomatic control of stridor.
- Consider ventilation during sleep (CPAP) as a first-line symptomatic therapy.
- Tracheostomy bypasses upper airway obstruction at laryngeal level and relieves distressing stridor. Tracheostomy is effective in the symptomatic control of stridor.
- Persistent and severe stridor may require tracheostomy.

CPAP for improving survival of patients with stridor

Statement is based on core literature consisting of Class III/IV level studies.^{8,10,12,13}

- Whether CPAP improves survival in patients with MSA with stridor is uncertain.

Tracheostomy for improving survival of patients with stridor

Statement is based on core literature consisting of Class III/IV level studies.^{8,10,11}

- Tracheostomy might improve survival in patients with stridor.

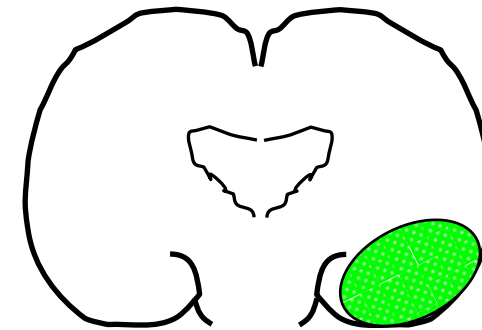
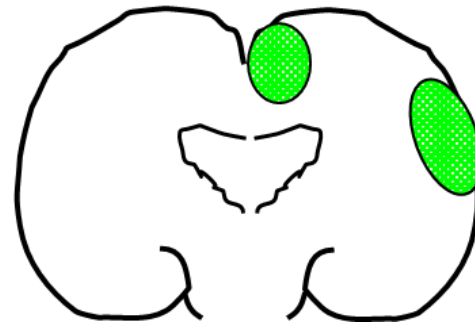
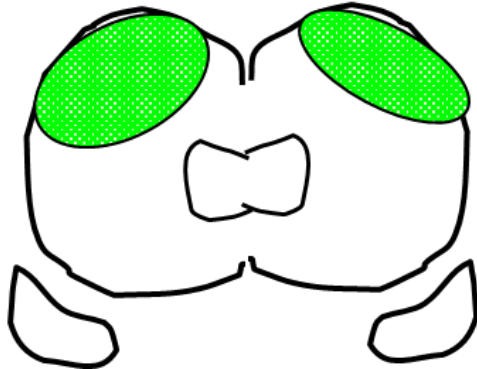
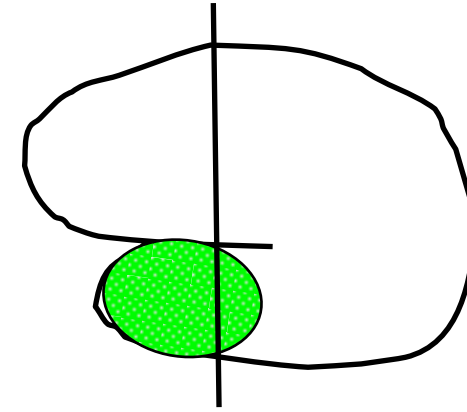
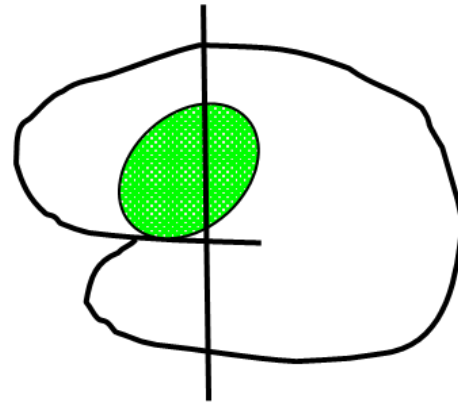
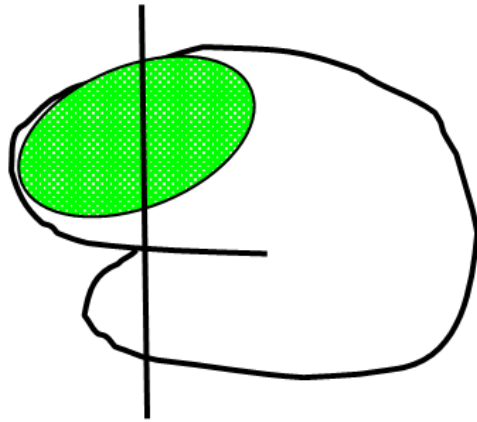
Key Sleep Issues in Select Neurodegenerative Disorders

bvFTD

- bvFTD/FTLD pathoanatomy
- Clinical and imaging features of bvFTD
- Key sleep issues

Key Sleep Issues in Select Neurodegenerative Disorders

FTD/PPA Pathoanatomy



bvFTD

nfvPPA

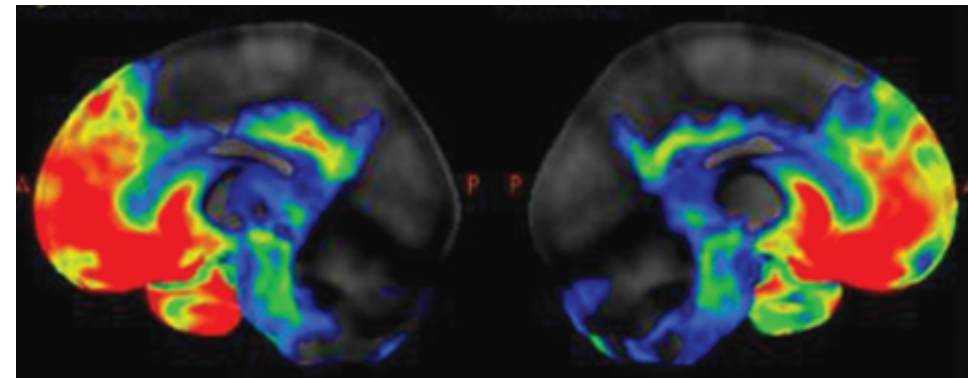
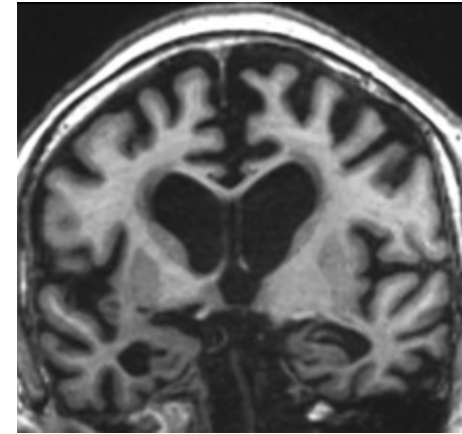
svPPA

Key Sleep Issues in Select Neurodegenerative Disorders

Clinical and Imaging Features of bvFTD

Core Clinical Features:

- behavioral disinhibition
- apathy
- loss of sympathy/empathy
- compulsive/ritualistic behavior
- hyper-orality/dietary changes
- executive dysfunction



Key Sleep Issues in Select Neurodegenerative Disorders

Key Sleep Issues in bvFTD

Sleep Disturbances in Frontotemporal Dementia

Stuart J. McCarter¹ • Erik K. St. Louis^{1,2,3} • Bradley F. Boeve^{1,3}

Sleep disorder	Frequency
Sleep disordered breathing (SDB)	68 %
Insomnia	48 %
Excessive daytime sleepiness (EDS)	64 %
Restless legs syndrome (RLS)	8 %
REM sleep behavior disorder (RBD)	Rare

Key Sleep Issues in Select Neurodegenerative Disorders


Key Sleep Issues in bvFTD

Sleep in Persons With Frontotemporal Dementia and Their Family Caregivers

Jennifer Merrilees ▼ Erin Hubbard ▼ Judy Mastick ▼ Bruce L. Miller ▼ Glenna A. Dowling

Nursing Res 2014

Sleep and circadian rhythm disruptions in behavioral variant frontotemporal dementia

Marco Filardi^{1,2}  | Valentina Gnoni² | Ludovica Tamburrino^{1,2} | Salvatore Nigro²
Daniele Urso² | Davide Vilella² | Benedetta Tafuri^{1,2} | Alessia Giugno² |
Roberto De Blasi^{2,3} | Stefano Zoccolella^{2,4} | Giancarlo Logroscino^{1,2}

Alz Dem 2024

Association of Changes in Cerebral and Hypothalamic Structure With Sleep Dysfunction in Patients With Genetic Frontotemporal Dementia

P. Tristin Best, MSc, John C. Van Swieten, MD, PhD, Lize Corrine Jiskoot, PhD, DClinPsy, Fermin Moreno, MD, PhD, Raquel Sánchez-Valle, MD, PhD, Robert Laforce, Jr., MD, PhD, Caroline Graff, MD, PhD, Mario Masellis, MD, PhD, Carmela Tartaglia, MD, James B. Rowe, PhD, Barbara Borroni, MD, Elizabeth Finger, MD, Matthias Synofzik, MD, Daniela Galimberti, PhD, Rik Vandenberghe, MD, PhD, Alexandre de Mendonça, MD, PhD, Christopher Butler, FRCP, PhD, Alexander Gerhard, MD, Isabelle Le Ber, MD, PhD, Pietro Tiraboschi, MD, Isabel Santana, MD, PhD, Florence Pasquier, MD, PhD, Johannes Levin, MD, Markus Otto, MD, Sandro Sorbi, MD, Harro Seelaar, MD, PhD, Arabella Bouzigues, MSc, David M. Cash, PhD, Lucy Louise Russell, PhD, Martina Bocchetta, PhD, Jonathan Daniel Rohrer, MRCP, Gabriel A. Devenyi, PhD, Mallar Chakravarty, PhD,* and Simon Ducharme, MD,* for the Genetic Frontotemporal Dementia Initiative (GENFI)

Correspondence

Mr. Best
paul.best@mail.mcgill.ca

Neurology 2024

Nocturnal sleep dynamics alterations in the early stages of behavioral variant frontotemporal dementia

Valentina Gnoni^{1,2,3,*} , Ludovica Tamburrino^{1,4}, Giulia Baldazzi^{5,6} , Daniele Urso^{1,2}, Stefano Zoccolella^{1,7}, Alessia Giugno¹, Michela Figorilli⁸, Salvatore Nigro¹, Benedetta Tafuri^{1,4}, Davide Vilella¹, Alessandra Vitulli¹, Chiara Zecca¹, Maria Teresa Dell'Abate¹, Danilo Pani^{5,6}, Monica Puligheddu⁸ , Ivana Rosenzweig^{2,3}, Marco Filardi^{1,4,†}  and Giancarlo Logroscino^{1,4,†}

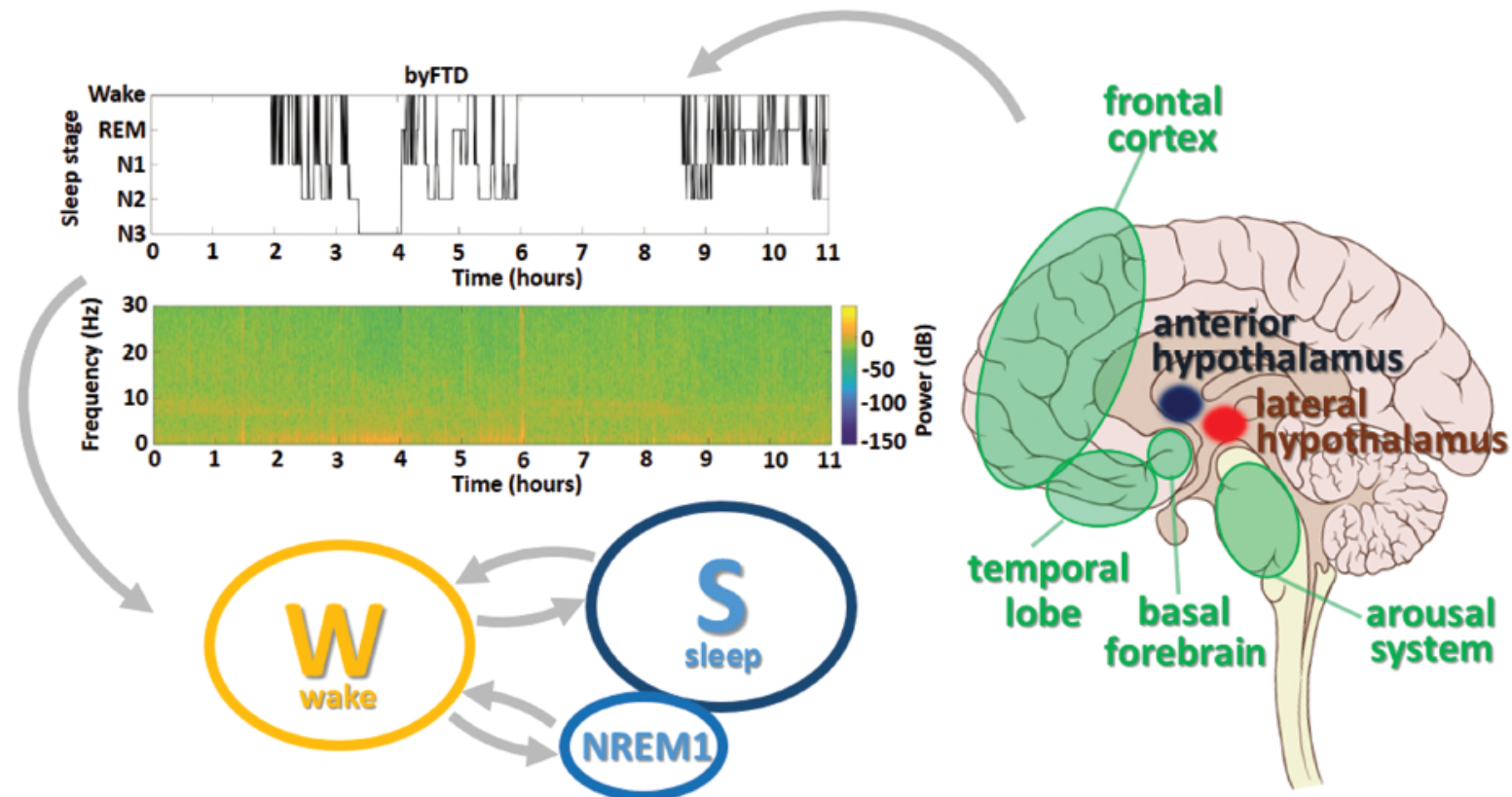
SLEEP 2025

Key Sleep Issues in Select Neurodegenerative Disorders

Key Sleep Issues in bvFTD

Nocturnal sleep dynamics alterations in the early stages of behavioral variant frontotemporal dementia

Valentina Gnani^{1,2,3,*}, Ludovica Tamburrino^{1,4}, Giulia Baldazzi^{5,6}, Daniele Urso^{1,2}, Stefano Zoccolella^{1,7}, Alessia Giugno¹, Michela Figorilli⁸, Salvatore Nigro¹, Benedetta Tafuri^{1,4}, Davide Vilella¹, Alessandra Vitulli¹, Chiara Zecca¹, Maria Teresa Dell'Abate¹, Danilo Pani^{5,6}, Monica Puligheddu⁸, Ivana Rosenzweig^{2,3}, Marco Filardi^{1,4,†} and Giancarlo Logroscino^{1,4,†}



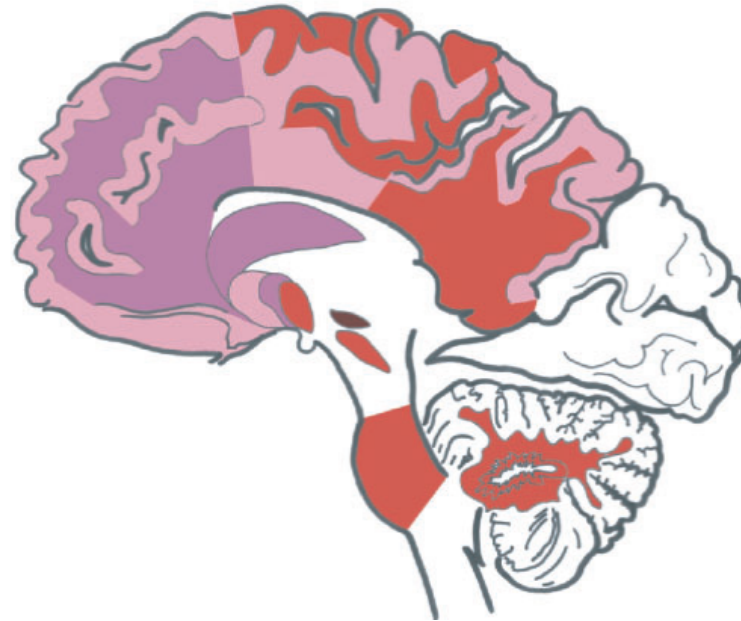
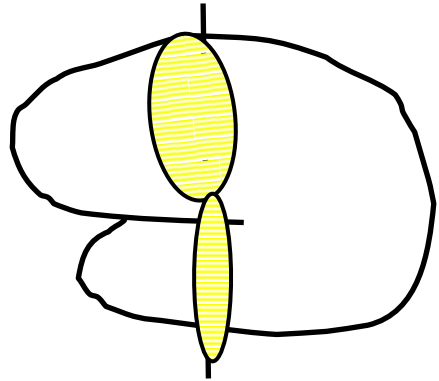
Key Sleep Issues in Select Neurodegenerative Disorders

Progressive Supranuclear Palsy

- PSP pathoanatomy
- Clinical and imaging features of PSP
- Key sleep issues

Key Sleep Issues in Select Neurodegenerative Disorders

PSP - Pathoanatomy



Key Sleep Issues in Select Neurodegenerative Disorders

PSP – Clinical and Neuroimaging Features

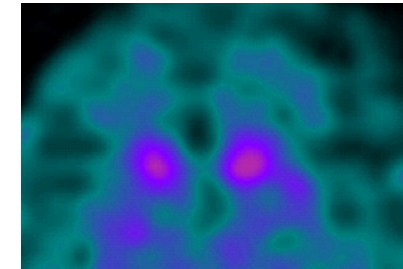
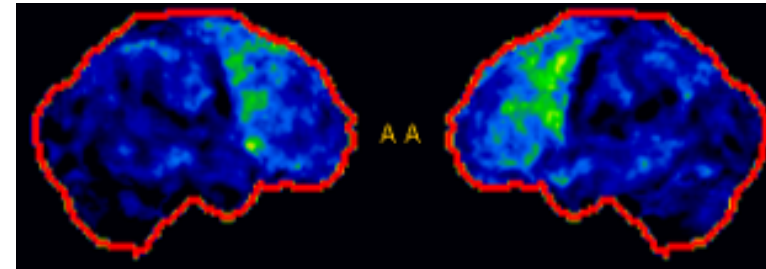
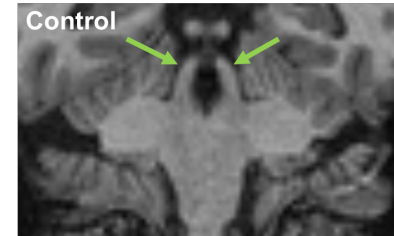
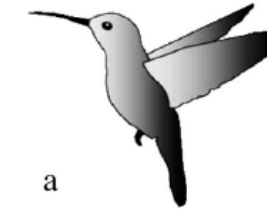
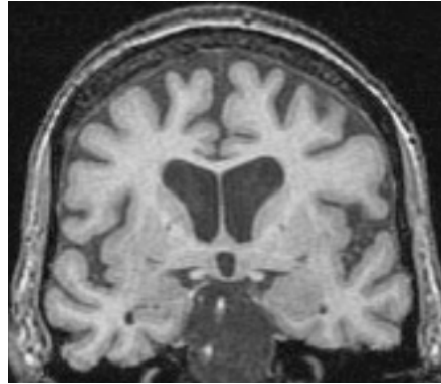
Core Clinical Features:

symmetric rigidity and bradykinesia
axial > appendicular
levodopa unresponsive

postural/gait instability
frequent falls

extraocular movement dysfunction
saccadic pursuits
delayed, slowed saccades
supranuclear gaze palsy, particularly downgaze

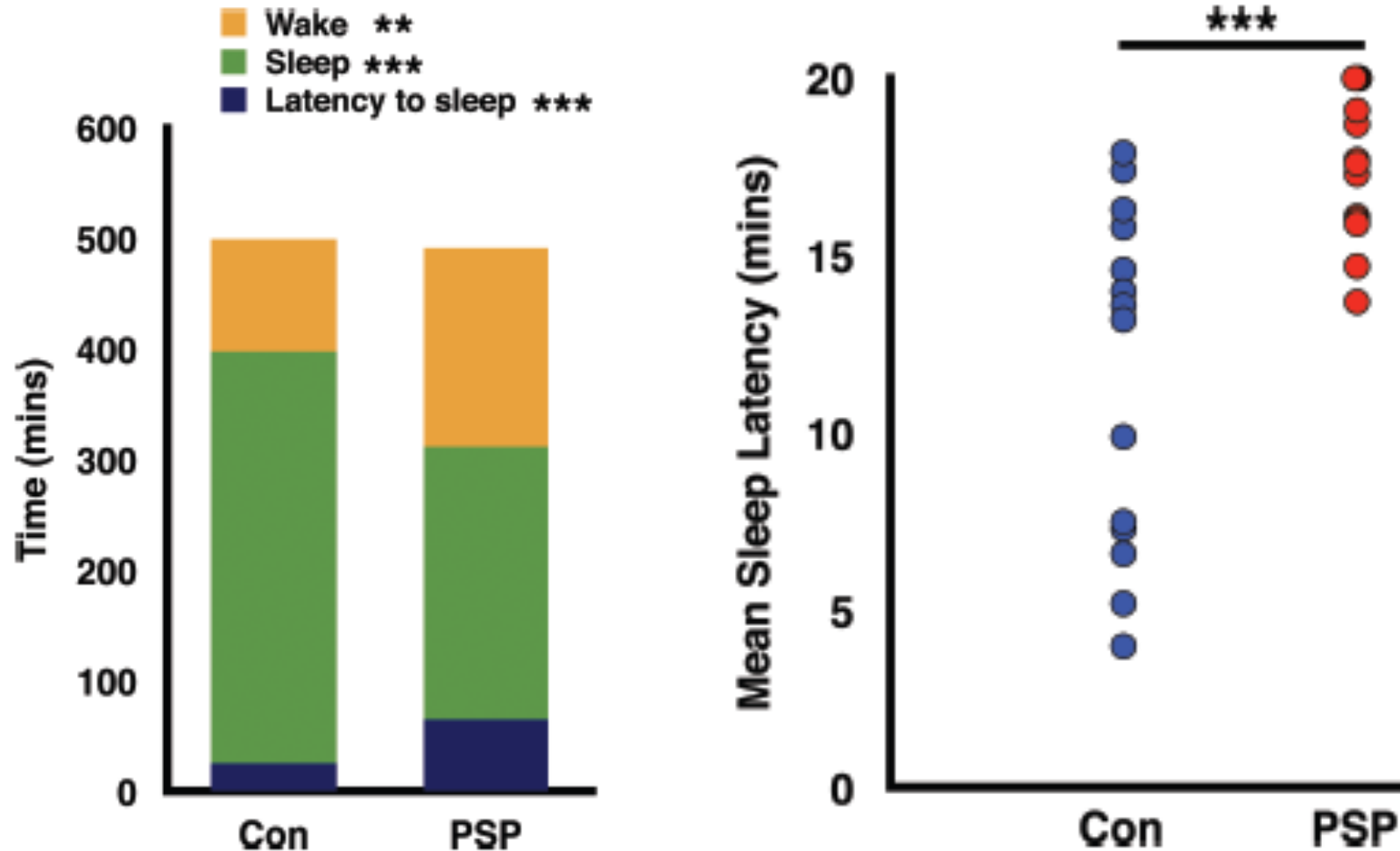
apathy, bradyphrenia



Key Sleep Issues in Select Neurodegenerative Disorders

PSP – Key Sleep Issues

Sleepless Night and Day, the Plight of Progressive Supranuclear Palsy

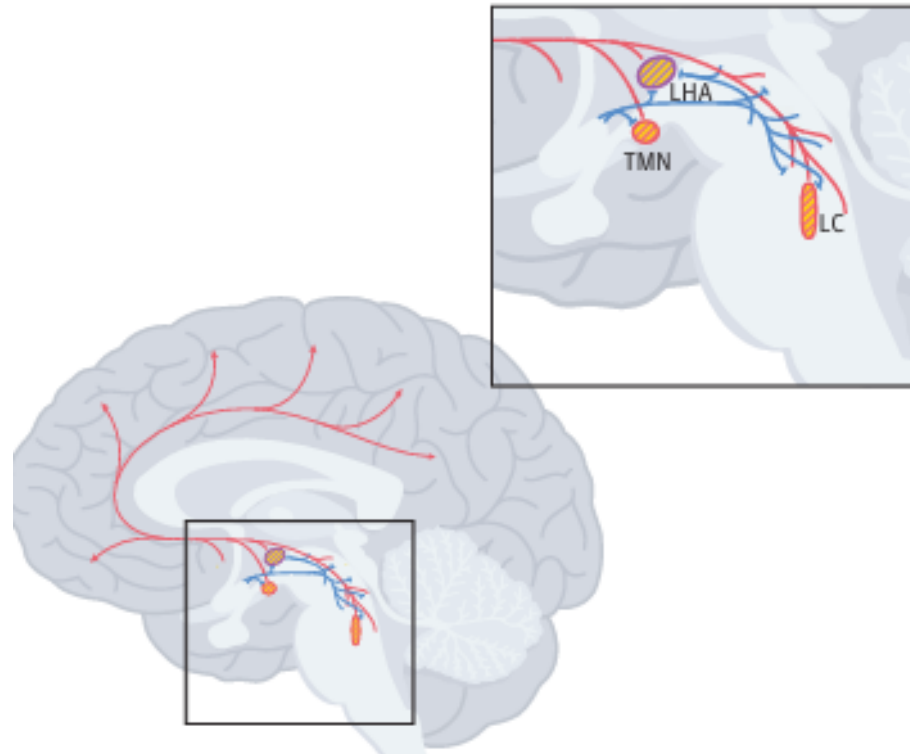


Key Sleep Issues in Select Neurodegenerative Disorders

PSP – Key Sleep Issues

Subcortical Neuronal Correlates of Sleep in Neurodegenerative Diseases

Jun Y. Oh, BA; Christine M. Walsh, PhD; Kamalini Ranasinghe, MBBS, PhD; Mihovil Mladinov, MD, PhD; Felipe L. Pereira, PhD; Cathrine Petersen, BA; Neus Falgàs, MD, PhD; Leslie Yack, BS; Tia Lamore, BA; Rakin Nasar, MS; Caroline Lew, PhD; Song Li, BS; Thomas Metzler, MA; Quentin Coppola, BS; Natalie Pandher, BS; Michael Le, BS; Hilary W. Heuer, PhD; Helmut Heinsen, MD; Salvatore Spina, MD, PhD; William W. Seeley, MD; Joel Kramer, PsyD; Gil D. Rabinovici, MD; Adam L. Boxer, MD, PhD; Bruce L. Miller, MD; Keith Vessel, MD; Thomas C. Neylan, MD; Lea T. Grinberg, MD, PhD



Number of neurons in LHA, TMN, and LC correlated with sleep-wake homeostasis.

AD – reduced neurons in these nuclei

PSP – neurons relatively preserved

Key Sleep Issues in Select Neurodegenerative Disorders

PSP – Key Clinical Trials

Treatment of Disturbed Sleep in Progressive Supranuclear Palsy (PSP)

ClinicalTrials.gov ID ⓘ **NCT04014387**

Sponsor ⓘ University of California, San Francisco

Information provided by ⓘ University of California, San Francisco (Responsible Party)

Last Update Posted ⓘ 2024-09-19

The Progressive Supranuclear Palsy Clinical Trial Platform (PTP)

Project Number

1R01AG085029-01

Contact PI/Project Leader

BOXER, ADAM L.

Other PIs

Key Sleep Issues in Select Neurodegenerative Disorders

Key Sleep Issues in ALS

Sleep disturbances in patients with amyotrophic lateral sclerosis: current perspectives

Boentert, Nature Sci Sleep 2019

Sleep and Sleep Disruption in Amyotrophic Lateral Sclerosis

Boentert, Curr Neurol Neurosc Rep 2020

Hypothalamus and amyotrophic lateral sclerosis: potential implications in sleep disorders

Gnoni et al, Front Aging Neurosci 2023

Pertinent sleep issues:

- Insomnia
- Daytime hypersomnia
- Sleep disordered breathing
- RLS
- PLMs
- RBD (rare)
- SRLC
- Pain

Key Sleep Issues in Select Neurodegenerative Disorders

Key Sleep Issues in Huntington's Disease

Sleep in Huntington's disease: a systematic review and meta-analysis of polysomnographic findings

Ye Zhang¹, Rong Ren¹, Linghui Yang¹, Junying Zhou¹, Yun Li², Jie Shi³, Lin Lu³, Larry D. Sanford^{4,*} and Xiangdong Tang^{1,*}

SLEEP 2019

Sleep Disorders and Circadian Disruption in Huntington's Disease

Sandra Saade-Lemus and Aleksandar Videnovic*

J Hunt Dis 2023

Sleep Dysfunction in Huntington's Disease: Impacts of Current Medications and Prospects for Treatment

Natalia E. Owen^{a,*}, Roger A. Barker^{a,b} and Zanna J. Voysey^a

J Hunt Dis 2023

Sleep in Neurodegenerative Disorders

Learning Objectives

Upon completion of this course, attendees should be able to:

- Describe updated concepts and terminology in neurodegenerative syndromes/diseases
- Describe key sleep issues in select neurodegenerative disorders
- Apply a practical approach to managing key sleep issues in neurodegenerative disorders
- Provide resources for fellow clinicians and patients/families

Practical Approach to Managing Sleep Issues in Neurodeg Dz

Outline

Symptom

- Insomnia
- Hypersomnia
- Excessive nocturnal motor activity
- Hallucinations/behavioral problems

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Insomnia

Etiology

- Underlying neurodegenerative dz
 - Any, but particularly PSP
- Primary sleep disorder
 - Particularly RLS
- Medical or other neuro disorder
 - BPH, pain
- Medication effect
 - Acetylcholinesterase inhibitors (AChEI)
 - Activating agents
- Depression
- Circadian dysrhythmia

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Insomnia

Etiology

- ***Underlying neurodegenerative dz***
- Primary sleep disorder - RLS
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- promote physical activity during day
- sufficient ambient light during day
- bright light therapy in am

- parkinsonism – dopaminergic agents

- trazodone
- melatonin or ramelteon
- z-agents
- DORAs

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Insomnia

Etiology

- Underlying neurodegenerative dz
- ***Primary sleep disorder - RLS***
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- may be challenging to diagnose
- consider checking ferritin, and if low, then treat
- dopaminergic agents (use with caution in those with psychosis)
- gabapentin, pregabalin
- clonazepam (in select pts)

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Insomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder - RLS
- ***Medical or other neuro disorder - BPH, pain***
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- evaluate cause for nocturia/frequency
- consider pain, and evaluate cause

- avoid agents with central anti-cholinergic properties
 - oxybutinin
- consider other options
 - trospium, mirabegron

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Insomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder – RLS
- Medical or other neuro disorder
- ***Medication effect - AChEI***
- Depression
- Circadian dysrhythmia

Management

- AChEI – take in am (not pm)
 - donepezil
 - rivastigmine
 - galantamine
- Avoid or reduce dose of selegiline

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Insomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder - RLS
- Medical or other neuro disorder
- Medication effect - AChEI
- ***Depression***
- Circadian dysrhythmia

Management

- Avoid “activating” agents
 - fluoxetine
 - venlafaxine
 - bupropion
- Avoid agents with prominent anti-cholinergic properties
 - amitriptyline, nortriptyline
 - paroxetine

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Insomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder - RLS
- Medical or other neuro disorder
- Medication effect - AChEI
- Depression
- ***Circadian dysrhythmia***

Management

- phototherapy
- melatonin at hs

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Hypersomnia

Etiology

- Underlying neurodegenerative dz
 - Any, but particularly PD and DLB
- Primary sleep disorder
 - Particularly OSA, CSA, CompSA, PLMs
- Medical or other neuro disorder
 - Many, including cancer
- Medication effect
 - Many
- Depression
- Circadian dysrhythmia

Practical Approach to Managing Sleep Issues in Neurodegen Dz Hypersomnia

Etiology

- ***Underlying neurodegenerative dz***
 - *Any, but particularly PD and DLB*
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- Diagnose and treat primary sleep d/o
- Promote daytime activity

- Wake-promoting agents/stimulants
 - modafinil
 - armodafinil
 - methylphenidate

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Hypersomnia

Etiology

- Underlying neurodegenerative dz
- ***Primary sleep disorder***
 - *Particularly OSA, CSA, CompSA, PLMs*
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- Do not assume those with dementia or parkinsonism cannot tolerate PAP therapy
- Diagnose and treat primary sleep d/o
- Threshold and efficacy for PLMD debated, but still worth considering treating

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Hypersomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- ***Medical or other neuro disorder***
 - *Many, including cancer*
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- Diagnose and treat medical issues
 - hypothyroidism
 - metabolic derangements
 - Infection
- While rare, consider CNS lesion

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Hypersomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- ***Medication effect***
 - ***Many***
- Depression
- Circadian dysrhythmia

Management

- Modify dosing of psychotropic agents
 - antidepressants
 - antipsychotics
 - dopaminergic agents
 - anxiolytics
 - anticonvulsants
- Note: AChEIs and memantine rarely cause hypersomnia

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Hypersomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- ***Depression***
- Circadian dysrhythmia

Management

- Avoid or reduce dosage of agents with sedating properties
- Considering use agents with “activating” properties
 - fluoxetine
 - venlafaxine
 - bupropion

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Hypersomnia

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- Depression
- ***Circadian dysrhythmia***

Management

- phototherapy
- stimulant in am
and/or
- melatonin at hs

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Excessive Nocturnal Motor Activity

Etiology

- Underlying neurodegenerative dz
 - Any, but particularly PD, DLB, MSA
- Primary sleep disorder
 - RBD
 - Sleep apnea and PLMs
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Excessive Nocturnal Motor Activity

Etiology

- ***Underlying neurodegenerative dz***
 - *Any, but particularly PD, DLB, MSA*
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- Consider PSG with video/ parasomnia protocol, even in advanced dementia and/or parkinsonism
- Ensure care partner present in room to promote safety, if feasible

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Excessive Nocturnal Motor Activity

Etiology

- Underlying neurodegenerative disease
- **Primary sleep disorder**
 - *Sleep apnea and PLMs*
 - *RBD*
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- Low threshold for PSG
- Diagnose and treat sleep apnea
- Consider treating PLMs
- RBD
 - usual non-Rx measures
 - melatonin
 - clonazepam
 - others

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Excessive Nocturnal Motor Activity

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- ***Medical or other neuro disorder***
 - *seizures*
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- PSG with video/parasomnia vs epilepsy montage
- Treat seizures if present
 - levetiracetam
 - lamotrigine
 - use classic agents with sedating properties carefully

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Excessive Nocturnal Motor Activity

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- ***Medication effect***
- Depression
- Circadian dysrhythmia

Management

- SSRI/SNRIs notorious for precipitating or aggravating RBD
- Tricyclics can aggravate PLMs
- AChEI dosed at night often increase RBD
- If depression - change SSRI/SNRI to another agent
 - Bupropion
- Dose AChEI in the morning

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Excessive Nocturnal Motor Activity

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- ***Depression***
- ***Circadian dysrhythmia***

Management

- As previously described

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Hallucinations/Behavioral Problems

Etiology

- Underlying neurodegenerative dz
 - Any, but particularly PD and DLB
- Primary sleep disorder
 - RBD
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia
 - Sundowning

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Hallucinations/Behavioral Problems

Dissociated states of wakefulness and sleep

Mark W. Mahowald, MD, and Carlos H. Schenck, MD

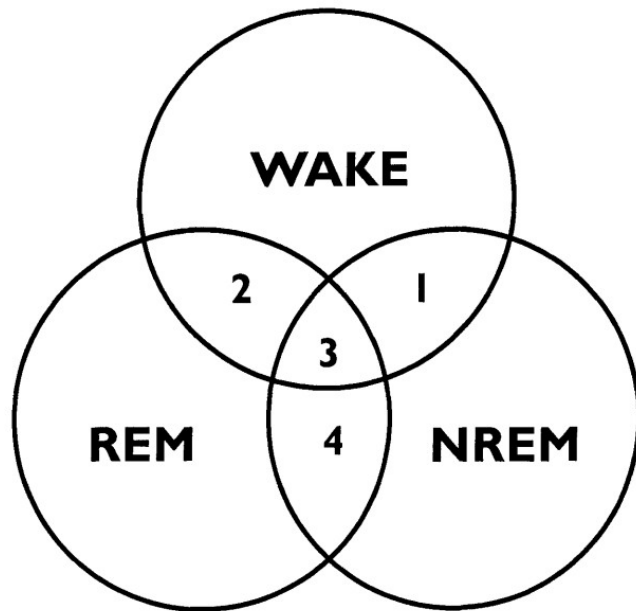


Figure 2. Areas of overlap among states:

1. Wake/NREM combinations
 - A. Disorders of arousal (sleepwalking, sleep terror, confusional arousals)
 - B. Psychogenic dissociation
2. Wake/REM combinations
 - A. Cataplexy, hypnagogic hallucinations, sleep paralysis
 - B. REM sleep behavior disorder
 - C. Lucid dreaming (out-of-body experiences)
 - D. Delirium (hallucinations—drug-induced/peduncular)
3. Wake/NREM/REM combinations
 - A. Status dissociatus
 - B. "Parasomnia overlap" syndromes
4. NREM/REM combinations

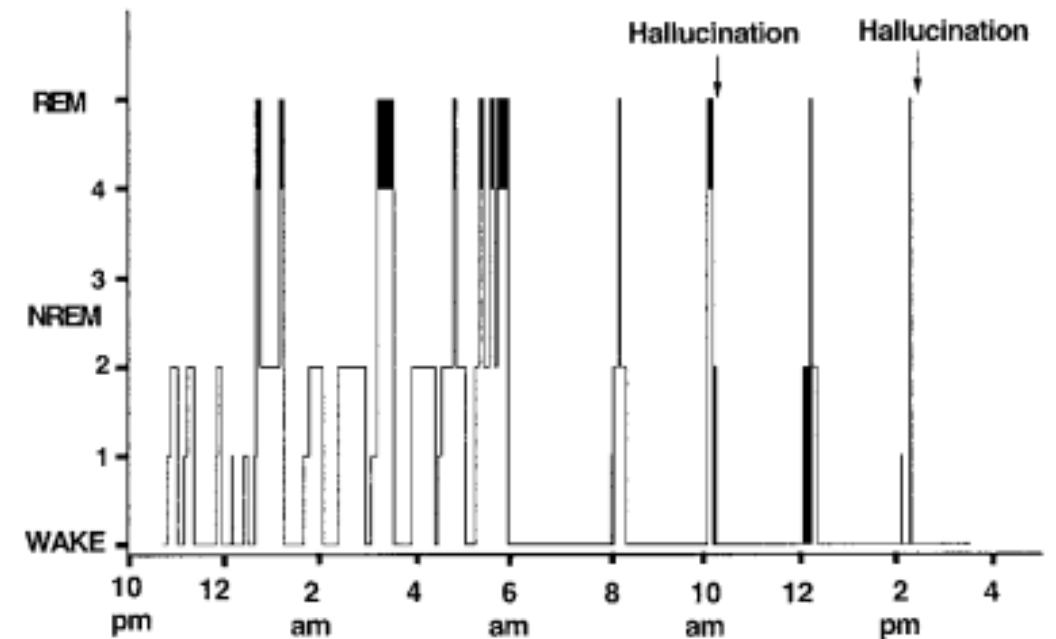
Theoretically possible, but not accompanied by conscious awareness

Neurology 1992

Hallucinations, REM sleep, and Parkinson's disease

A medical hypothesis

I. Arnulf, MD; A.-M. Bonnet, MD; P. Damier, MD, PhD; B.-P. Bejjani, MD; D. Seilhean, MD; J.-P. Derenne, MD; and Y. Agid, MD, PhD



Neurology 2000

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Hallucinations/Behavioral Problems

Etiology

- ***Underlying neurodegenerative dz***
 - *Any, but particularly PD and DLB*
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- Depression
- Circadian dysrhythmia

Management

- ? REM sleep intrusions into wakefulness
- Endorsement, redirection, “therapeutic fibs”
- Rx considerations
 - Reduce dose or eliminate dopaminergics, selegiline, amantadine
 - AChEI if not already being used
 - melatonin if not already being used
 - quetiapine, clozapine, pimavanserin
 - mood stabilizers

Practical Approach to Managing Sleep Issues in Neurodegenerative Disease

Hallucinations/Behavioral Problems

Etiology

- Underlying neurodegenerative dz
- ***Primary sleep disorder***
 - ***RBD***
- ***Medical or other neuro disorder***
- ***Medication effect***
- ***Depression***
- Circadian dysrhythmia
 - Sundowning

Management

- Dx and Tx RBD
- Dx and Tx medical issues
- Adjust dopaminergics
- Avoid agents with anticholinergic properties

Practical Approach to Managing Sleep Issues in Neurodeg Dz

Hallucinations/Behavioral Problems

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- Depression
- ***Circadian dysrhythmia***
 - ***Sundowning***

Considerations

- “sundowning” - term that implies problem symptoms or behaviors develop during the evening or night
- data supporting behaviors are more frequent in evening/night is mixed
- “some components of sundowning may reflect disruptive behaviors occurring with identical frequency throughout the day but with differential impact upon caregivers or nursing staff”

Practical Approach to Managing Sleep Issues in Neurodegen Dz

Hallucinations/Behavioral Problems

Etiology

- Underlying neurodegenerative dz
- Primary sleep disorder
- Medical or other neuro disorder
- Medication effect
- Depression
- ***Circadian dysrhythmia***
 - ***Sundowning***

Management

- caregiver education, psychological support, time away from patients via respite care, etc.
- choose Rx directed toward specific behaviors (as discussed in previous slides)

Sleep in Neurodegenerative Disorders

Learning Objectives

Upon completion of this course, attendees should be able to:

- Describe updated concepts and terminology in neurodegenerative syndromes/diseases
- Describe key sleep issues in select neurodegenerative disorders
- Apply a practical approach to managing key sleep issues in neurodegenerative disorders
- Provide resources for fellow clinicians and patients/families

Resources/Support

