Sleep and Neurodegeneration

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Topic Outline

- **Sleep disturbances in patients with neurodegenerative diseases**
  - PD
  - Non-PD (AD and the others)
- **OSA and dementia**
- **REM behavior disorders**
- **Diagnostic approaches**

Dementia: Neuropathologic Classification

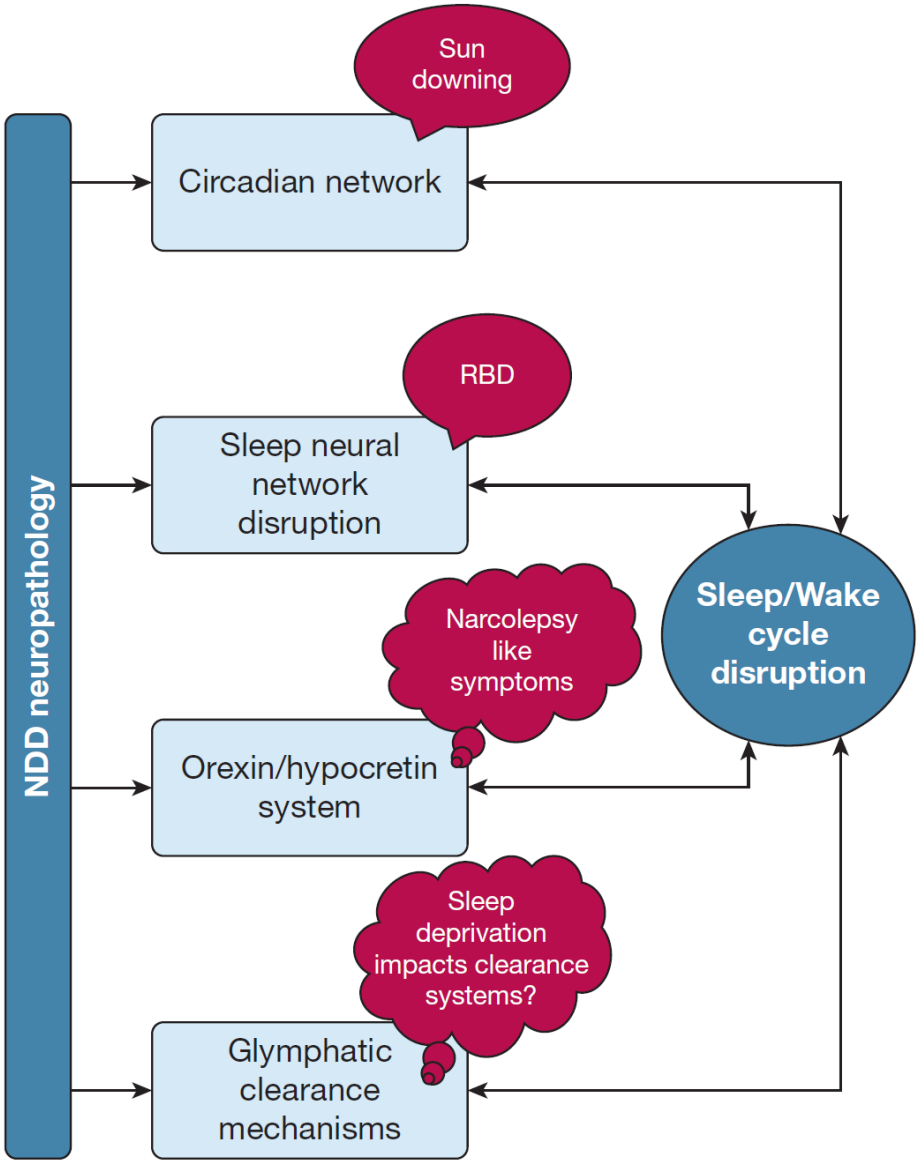
Tauopathies

- Alzheimer's disease
- Frontotemporal dementia
- Progressive supranuclear palsy
- Corticobasal degeneration
- Frontotemporal degeneration

α-Synucleinopathies

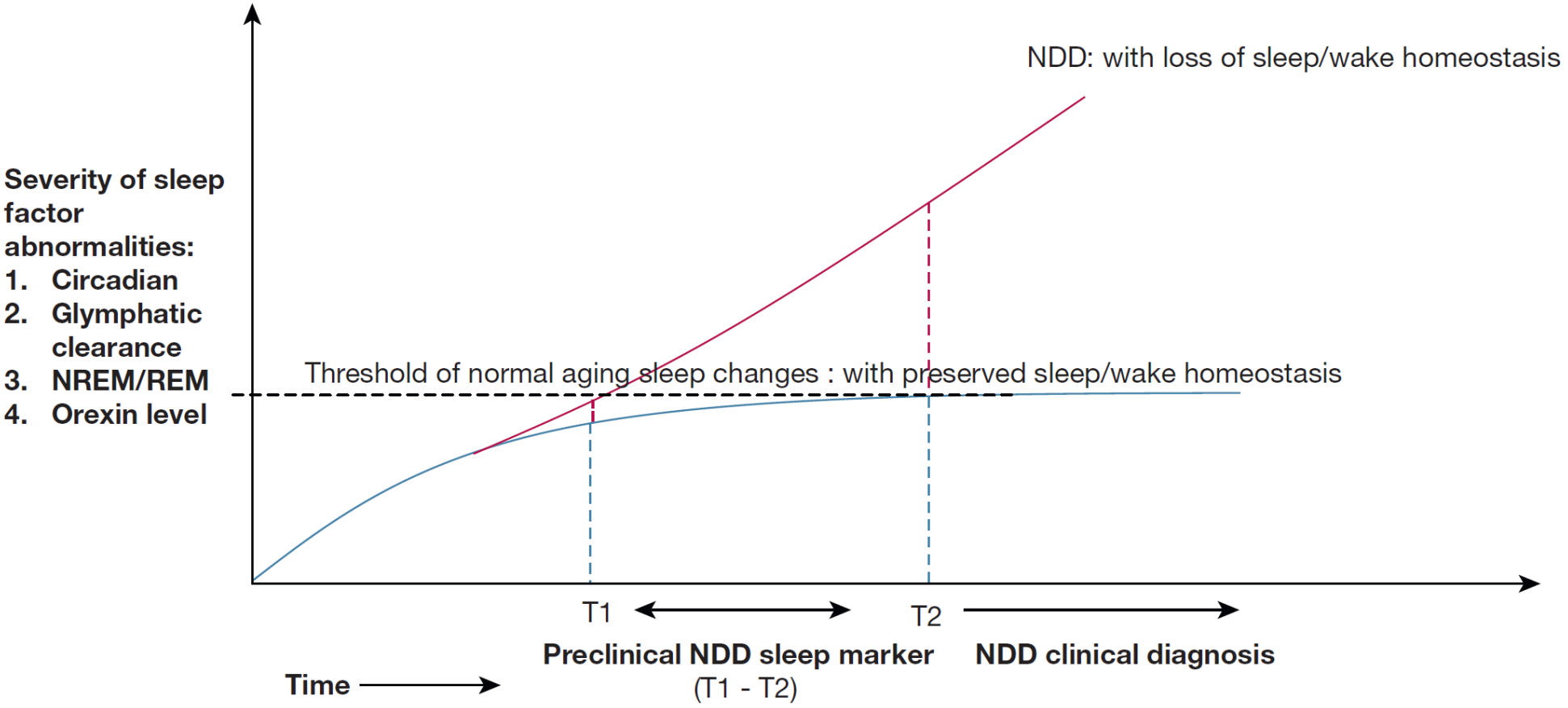
- Parkinson’s disease
- Dementia with Lewy bodies
- Multiple system atrophy
- Neurodegeneration with brain iron accumulation, type 1

Interacting pathways of NDD pathology and sleep/wake disruption



Pillai JA. CHEST 2017; 151(6):1375-1386

Hypothetical model for sleep factor abnormalities with loss of homeostatic regulation in NDDs



Pillai JA. CHEST 2017; 151(6):1375-1386

Sleep and Alertness in PD

- Sleep disturbances in PD are classified into two broad categories:
  - Disorders of nocturnal sleep - insomnia, REM sleep behavior disorder, sleep apnea, and restless legs syndrome/periodic limb movement disorder (RLS/PLMD)
  - Daytime alertness - excessive daytime somnolence, sleep attacks

Causes of Sleep Disturbances in Parkinson's Disease

- **1. PD-related pathological changes**
  - Impairment of sleep architecture (REM and non-REM sleep)
  - Impairment of the arousal system (orexin, serotonin, noradrenalin, acetylcholine, and dopamine)
  - Impairment of the sleep-wake cycle, circadian rhythm sleep disorder, sundown syndrome
- **2. Nocturnal motor symptoms**
  - Wearing off phenomenon, rigidity, akinesia, tremor, medication-related dyskinesia, and dystonia
- **3. Nocturnal non-motor symptoms**
  - Neuropsychiatric symptoms (depression, psychosis, cognitive impairment)
  - Sensory symptoms (pain, dysesthesia, restlessness of the arms or legs)
  - Hallucinations
  - Nightmares and vivid dreams
  - Nocturia
- **4. Medication use**
  - Dopaminergic drugs, antipsychotics
- **5. Comorbid primary sleep disorders**
  - Sleep apnea syndrome
  - REM sleep behavior disorder
  - Restless legs syndrome, periodic limb movements

Suzuki K, et al. doi:10.5772/57320.

Rating scales and questionnaires for assessment of sleep disorders in Parkinson's disease

- Specific 'Recommended' scales
  - Parkinson's Disease Sleep Scale (PDSS)
  - PDSS-2
  - Scales for Outcomes in PD-Sleep (SCOPA-Sleep)
- Generic 'Recommended' scales
  - Pittsburgh Sleep Quality Index (PSQI)
  - Epworth Sleepiness Scale (ESS)
- 'Suggested' scales
  - Inappropriate Sleep Composite Score (ISCS) questionnaire
  - Stanford Sleepiness Scale

Circadian Rhythm Dysfunction In PD

- Circadian rhythmicity: associated with reduced nighttime sleep quality, daytime alertness and cognitive performance

- Mechanisms:
  - Dopamine is a likely mediator of light signaling to the retinal circadian clock which provides direct input to the SCN
  - Fluctuations in dopamine metabolism, overnight dopamine accumulation or diurnal receptor downregulation may be in part driving these fluctuations
  - Neuroanatomical sites of circadian disruption in PD may be along the afferent pathways to the SCN, within the SCN itself, or within the downstream peripheral efferents of the SCN.

Witkovsky, P. Ophthalmol. 2004:108;17–40.

Insomnia

- Most common sleep disturbances in PD patients
  - Difficulty maintaining asleep
  - Multifactorial in etiology - overnight emergence of motor symptoms, pain, nocturia, coexistence of other sleep disorders: SDB, PLMD.

- Nocturia (voiding ≥2 times per night) - 80% of PD patients, increases with PD severity and duration.

- Depression - contribute to sleep disturbances, correlate with sleep initiation and maintenance difficulties.

- Nocturnal hallucinations - 20% of PD patients, provoked by PD medications, infection, use of sedatives, electrolyte imbalance. More common in advanced disease and in patients with underlying cognitive impairment.

- Published data failed to demonstrate a direct correlation between poor nocturnal sleep and excessive daytime somnolence (EDS) in PD

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Insomnia: Practical Points

- Improved control of nighttime motor symptoms of PD.
  - long acting formulation of levodopa at bedtime.
  - Addition of a cathechol-O-methyltransferase (COMT) inhibitor to the nighttime levodopa dose.
  - Use of a long-acting dopamine agonist.
  - Use of an additional dose of levodopa in the middle of the night.
  - Taken selegiline and amantidine taken earlier in the day.

- Nocturia patients
  - Minimize evening fluid intake
  - Use the bathroom before going to the bed
  - Use a bedside commode during the night.
  - Earlier scheduled diuretic medications.
  - Anticholinergic medications

- Identification and proper treatment of psychiatric comorbidities

- Placed on diagnosis of primary sleep disorders

Insomnia: Treatment in PD

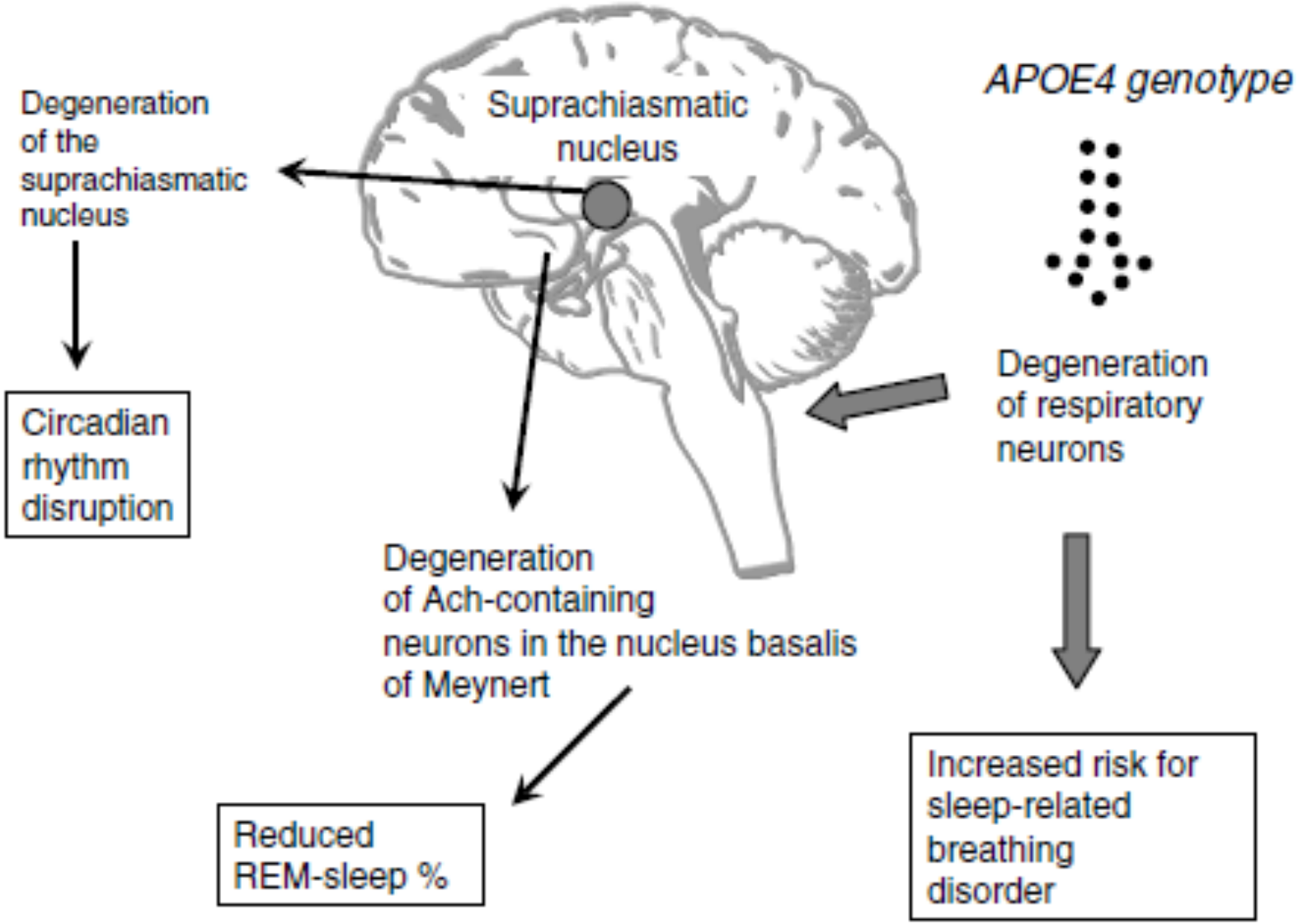
- CBT-I in combination with bright light therapy
  - Significant improvement in several subjective measures of insomnia severity but worsening in UPDRS and Parkinson's Disease Questionnaire (PDQ) 39-item.
  - Increased "awareness of self" developed during CBT may have made patients more aware of their disease-related limitations
- Doxepin (10 mg at bedtime) - Insomnia Severity Index and the Scales for Outcomes in Parkinson's Disease-night scale at 6 weeks
  - Significant benefit, including the Fatigue Severity Scale.
  - No significant worsening in measures of daytime sleepiness and a significant improvement in MoCA scores.
- Amitriptyline – no systematically studied data
- Trazodone - improvement in UPDRS and depression but increased rates of hip fracture or falls, dysequilibrium, impairments in short-term memory, and worsening verbal memory
- Melatonin (3 mg) – limited data
- Quetiapine – no benefit

Management of Sleep Problems in Patients with Parkinson's Disease

Type of insomnia	Cause	Treatment
Difficulty initiating sleep	Unknown cause	Hypnotics (short-acting type; eszopiclone, zolpidem, zopiclone, brotizolam)
	Drug-related (alerting effect)	Remove or reduce dose of causative drug
Difficulty maintaining sleep/early morning awakening	Unknown cause	Hypnotics (intermediate type; flunitrazepam)
	Wearing off, resting tremor, rigidity, akinesia	Increase frequency of levodopa administration, add dopamine agonist, or switch to a different type of dopamine agonist
	Drug-induced dyskinesia	Increase frequency of levodopa and reduce dose of levodopa administration, add dopamine agonist
	Depression, anxiety	Antidepressant (SSRI, SNRI, tricyclic antidepressant)
		Antianxiety drug
		Dopamine agonist (D3 R)
	Nocturia	Oxybutynin, flavoxate
		Dopamine agonist (D1 R)
Excessive daytime sleepiness	Unknown cause	Daytime rehabilitation
	Drug-related (sedative effect)	Remove or reduce dose of causative drug (including dopamine agonist)
	Refractory	Modafinil, caffeine
Hallucinations, delusions, delirium		Reduce dopaminergic drugs, consider Yi-Gan San[a] and atypical antipsychotics
REM sleep behavior disorder		Hazard avoidance (remove potentially dangerous objects from the bedroom and place a mattress on the floor), consider clonazepam and Yi-Gan San[a]
Sleep apnea syndrome		Continuous positive airway pressure therapy (severe case)
Restless legs syndrome, periodic limb movements		Adjustment of dopaminergic treatment, use dopamine agonist and/or clonazepam prior to bedtime, consider iron supplement (if serum ferritin levels are below 50 μg/L) Gabapentin, pregabalin, gabapentin enacarbil, or opioids may be alternatively used

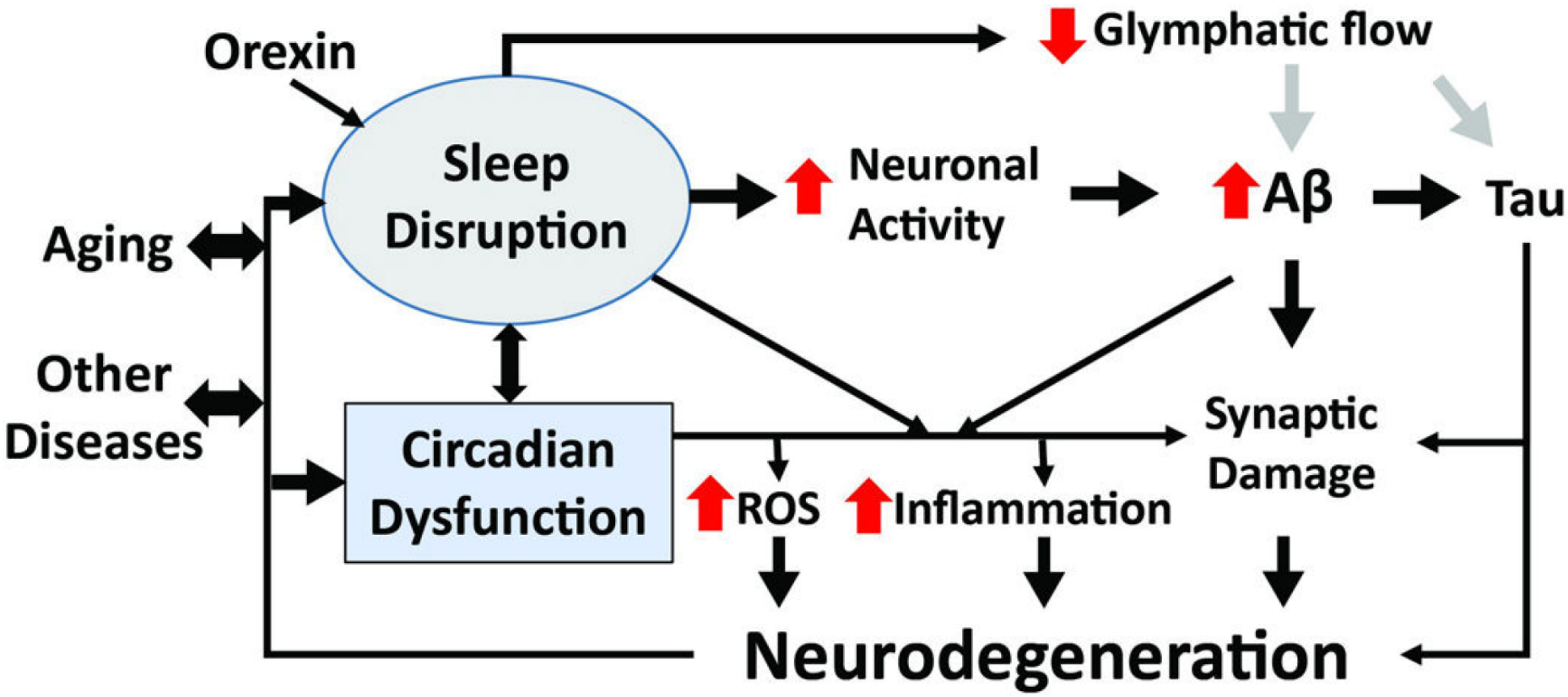
Suzuki K, et al. doi:10.5772/57320.

Pathogenesis of Sleep Disturbances in AD



Avidan AY. Semin Neurol. 2005 Mar;25(1):52-63.

Proposed mechanisms linking sleep loss, Aβ, and neurodegeneration in AD



Sleep disorders in Alzheimer disease

- Sleep disorders are common, affecting up to 45% of patients having an important impact on patients and caregivers.

- Sleep disorders may be an early manifestation but their frequency and intensity usually progress with disease severity.

- The most common sleep problem is an exaggerated tendency to **phase advancing** characterized by frequent daytime napping, difficulties in falling asleep at night, nocturnal sleep fragmentation, and early morning awakening. This pattern is similar but more severe than that seen in the elderly.

Peter-Derex L. Sleep Med Rev 2015;19:29–38.

Sleep disorders in Alzheimer disease

- The **sundowing syndrome**, which is characterized by agitation, confusion, and aggressiveness in the dark hours of the evening and in the night.

- In the middle of the night patients may experience **confusional awakenings** with nocturnal wandering and agitation.

Peter-Derex L. Sleep Med Rev 2015;19:29–38.

Sleep disorders in Alzheimer disease

- Polysomnography shows
  - reduced total sleep time and sleep efficiency, increased sleep-onset latency and wake time after sleep onset, reduced deep sleep and REM sleep amounts, and increased light sleep amount. In advanced cases sleep scoring is difficult because of the absence of alpha rhythm during wakefulness and loss of sleep spindles and K complexes.

- RBD is very rare.

- RLS seems to be not prominent, although its frequency may be underestimated because diagnosis requires patients describing their sensations in the legs. Specific RLS criteria for dementia have been developed.

- The frequency of OSA is high affecting between 40% and 70% and may aggravate cognitive dysfunction in AD.

Peter-Derex L. Sleep Med Rev 2015;19:29–38.

Sleep disorders in Alzheimer disease

- Management of sleep disorders is based in cognitive-behavioral strategies, sleep hygiene, and bright light therapy.

- In early stages acetylcholinesterase inhibitors may ameliorate the sleep pattern and cognition.

- Continuous airway pressure therapy is indicated in OSA. Although robust scientific evidence is lacking, several medications are commonly used to enhance sleep, such as melatonin, benzodiazepines, sedating antidepressants, and atypical neuroleptics (eg, quetiapine).

Peter-Derex L. Sleep Med Rev 2015;19:29–38.

Sleep disorders in dementia with Lewy bodies

- Sleep disorders affect about 80% of the patients and are more frequent than in AD.
- Insomnia, circadian rhythm disorder with early awakening, EDS caused by frequent napping, nocturnal hallucinations, and confusional nocturnal wandering are frequent.
- Confusional nocturnal awakenings usually arise from non-REM sleep stages.
- OSA, PLMS, and RLS are no more common than in the general population of similar age.

Sleep disorders in multiple system atrophy

- About 70% of patients with MSA report sleep problems.
- Sleep-onset insomnia and fragmented sleep occur in about 50%. Many causes may contribute to sleep fragmentation and include urinary incontinence, anxiety, depression, inability to change body position in the bed because of parkinsonism, and the use of several medications.
- EDS occurs in 28% but in most is not a major complaint. In a few patients sleep attacks may occur after the intake of levodopa.

Sleep disorders in multiple system atrophy

- It is not clear if RLS and PLMS are more frequent than in the general population of similar age.

- MSA is eventually diagnosed in only a few subjects with the initial diagnosis of idiopathic RBD (most of them are diagnosed with PD and dementia with Lewy bodies), probably because in the general population MSA is much less common than PD and dementia with Lewy bodies.

- RBD occurs in 80% to 100%. In a patient with suspected MSA, the absence of RBD should seriously question the diagnosis of this disease.

Sleep disorders in multiple system atrophy

- In about half of the patients, RBD precedes the cardinal symptomatology of the disease.
- Breathing problems may be of central and peripheral (obstructive) origin.
- Central respiratory disturbances are caused by degeneration of the bulbar respiratory centers leading to abnormal hypoxic ventilatory responses, Cheyne-Stokes respiration, irregular breathing, and central sleep apnea.

Sleep disorders in multiple system atrophy

- Nocturnal stridor occurs in about 20% of the patients.
  - One of the red flags that should raise suspicion of MSA in a patient with parkinsonism.
  - Occurs in all stages of the disease and indicates obstruction of the airway at the level of the vocal cords in the larynx.
  - As the disease advances, nocturnal stridor progresses into wakefulness because of an increasing reduction in the glottic aperture.

- Patients with MSA, particularly those with stridor, may present typical OSA episodes with oxyhemoglobin desaturations and in some cases subacute episodes of respiratory failure.

Sleep disorders in multiple system atrophy

- In most patients with nocturnal stridor the clinical examination of the vocal cords during wakefulness with laryngoscopy shows vocal cord paralysis.

- The presence of stridor in MSA has been linked to decreased survival and sudden death during sleep.

- Nasal continuous positive airway pressure and tracheostomy eliminate stridor and obstructive apneas in MSA.

Sleep disorders in progressive supranuclear palsy

- Polysomnographic studies show reduced total sleep time, decreased REM sleep percentage, and reduction in sleep spindles and K complexes. In severe cases the alpha rhythm is absent and wakefulness and sleep stages are difficult to differentiate.

- The most frequent sleep complaint is insomnia with difficulty in falling sleep and maintenance of sleep, and sometimes symptoms suggestive of RBD. In some patients, RBD-like symptoms may reflect true nocturnal wandering and confusional awakenings, which are frequent in patients with any type of dementia.

Sleep disorders in progressive supranuclear palsy

- EDS, OSA, PLMS, and RLS are not major complications in PSP.
- RBD occurs in about 10% to 20% and is usually of mild severity and frequently develops after dementia onset.
- The subclinical form of RBD (asymptomatic REM sleep without atonia) occurs in about 20%.

Sleep disorders in Huntington disease

- Sleep disorders affect up to 87% of the cases, particularly in advanced stages. Sleep complaints increase with disease severity and duration.

- Patients usually report poor sleep quality, insomnia, sleep fragmentation with frequent awakenings at night, EDS, and the circadian rhythm sleep disorder of the advanced phase type resulting in early morning awakening.

Sleep disorders in Huntington disease

- Polysomnographic studies show reduced sleep efficiency, increased wake time after sleep onset, increased percentage of light sleep, increased REM sleep latency, and reduced percentage of deep sleep and REM sleep.

- RBD, OSA, and RLS may occur but they are not frequent or a major problem.

Sleep in hereditary spinocerebellar ataxias

- OSA and EDS are not common.
- Nocturnal stridor caused by vocal cord abnormalities has been described in spinocerebellar ataxias (SCA) 1 and SCA3.
- RBD occurs in up to 50% of patients with SCA3 (Machado-Joseph disease) and in patients with SCA2 but with mild clinical severity. RBD has not been found in SCA2.
- RLS has been described in SCA1, SCA2, SCA3, and SCA6.

Sleep disorders in amyotrophic lateral sclerosis

- Loss of motor neurons in the brainstem and spinal cord results in pharyngeal, laryngeal, diaphragmatic, and intercostal muscle weakness that predispose to respiratory dysfunction.

- The most common sleep abnormality is respiratory dysfunction.

- Sleep-disordered breathing occurs in 17% to 76%, and includes nocturnal alveolar hypoventilation, OSA, laryngeal stridor, and central sleep apnea. The most common form is nocturnal hypoventilation caused by palsy of the diaphragmatic, intercostal, and accessory respiratory muscles.

Sleep disorders in amyotrophic lateral sclerosis

- Sleep apnea occurs less frequently than hypoventilation. Most apneic events are central because diaphragmatic weakness and palsy of respiratory accessory muscles predispose to this form of sleep apnea.

- Nocturia, muscle cramps, sleep-onset insomnia, reduced sleep amount, and EDS are the main sleep complaints.

- RBD and RLS are not frequent but they may occur.

OSAS : Diagnostic Criteria

- **(A and B), or C**

- **A. The presence one or more of the following:**

1. The patient complaints of sleepiness, nonretorative sleep, fatigue, or insomnia symptoms.
2. The patient wakes with breath holding, gasping, or choking
3. The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep
4. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus.

OSAS : Diagnostic Criteria

- **B. Polysomnography (PSG) or OCST demonstrates:**
  1. Five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or RERAs)/hr of sleep

- **C. PSG or OCST demonstrates:**
  1. Fifteen or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or RERAs)/hr of sleep.

Medical Consequences

Neurobehavioral derangement

- Excessive daytime sleepiness
- Depression
- Impotence
- Personality change, irritability
- Learning and memory difficulties
- Morning headache
- Lack of energy
- Decreased work performance
- Traffic accident

Cardiopulmonary derangement

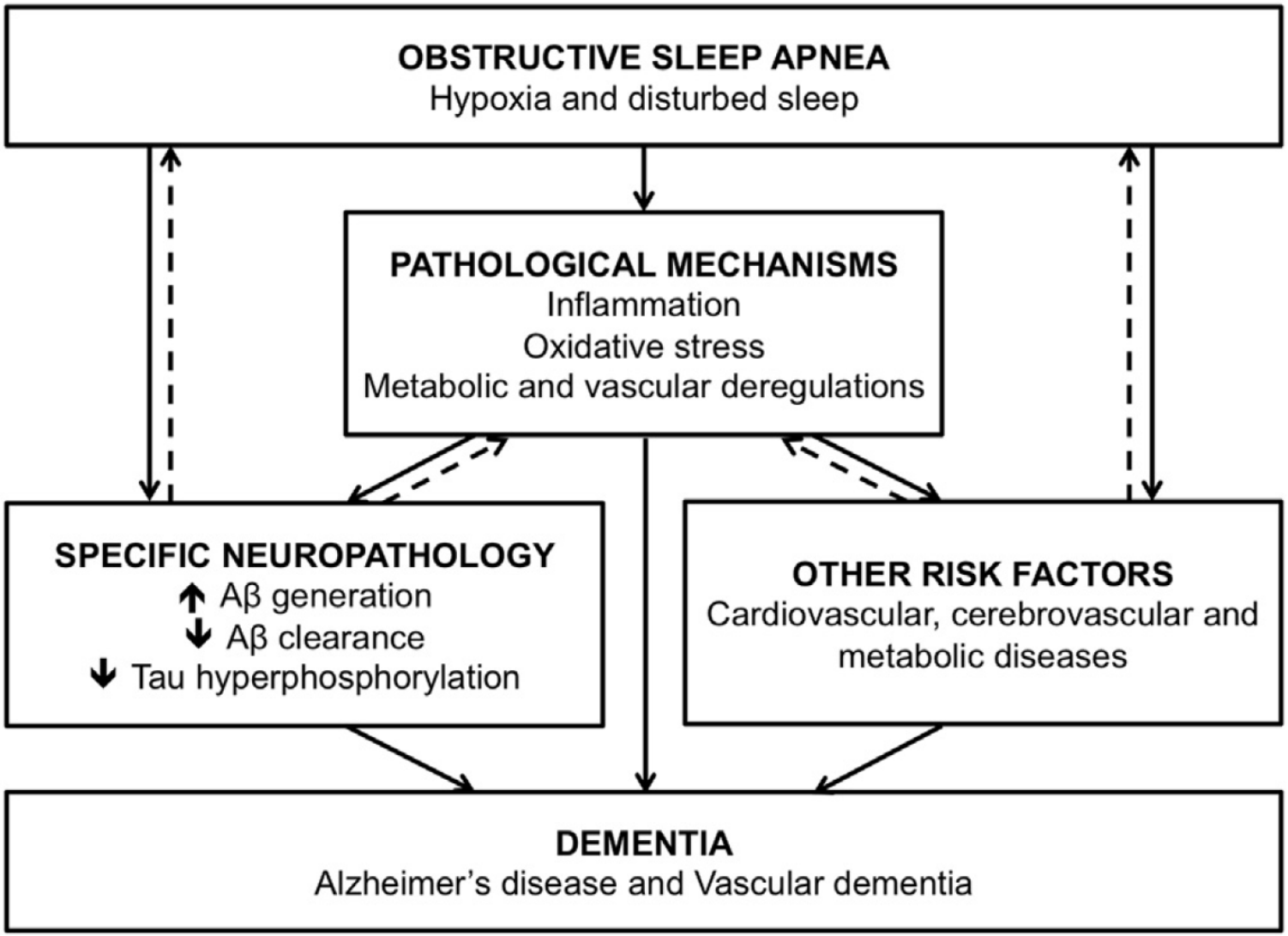
- Hypertension
  - Occur in 50% OSA patients
  - About 30% of HT have OSA
- Repetitive hypoxia and hypercapnia at night may contribute to increase in sympathetic tone resulting in HT.
- RV hypertrophy and failure
- Cardiac arrhythmias

Dementia and OSA

- An emerging modifiable risk factor for dementia including MCI.
- Mainly focus on AD and VaD.
- No association between APOE polymorphism and the presence of OSA. However, the APOE4 allele may interact with OSA to worsen cognitive performance: OSA severity was associated with worse memory, attention, executive functioning as well as worse global cognition only in APOE4 carriers.
- OSA severity indices were not associated with CSF Ab42 levels at cross-section but correlated with annual rates of CSF Ab42 level decrease over the two-year follow-up, which would be consistent with increases in amyloid burden over time.
- CPAP slows the rate of cognitive decline over three years (MMSE score).

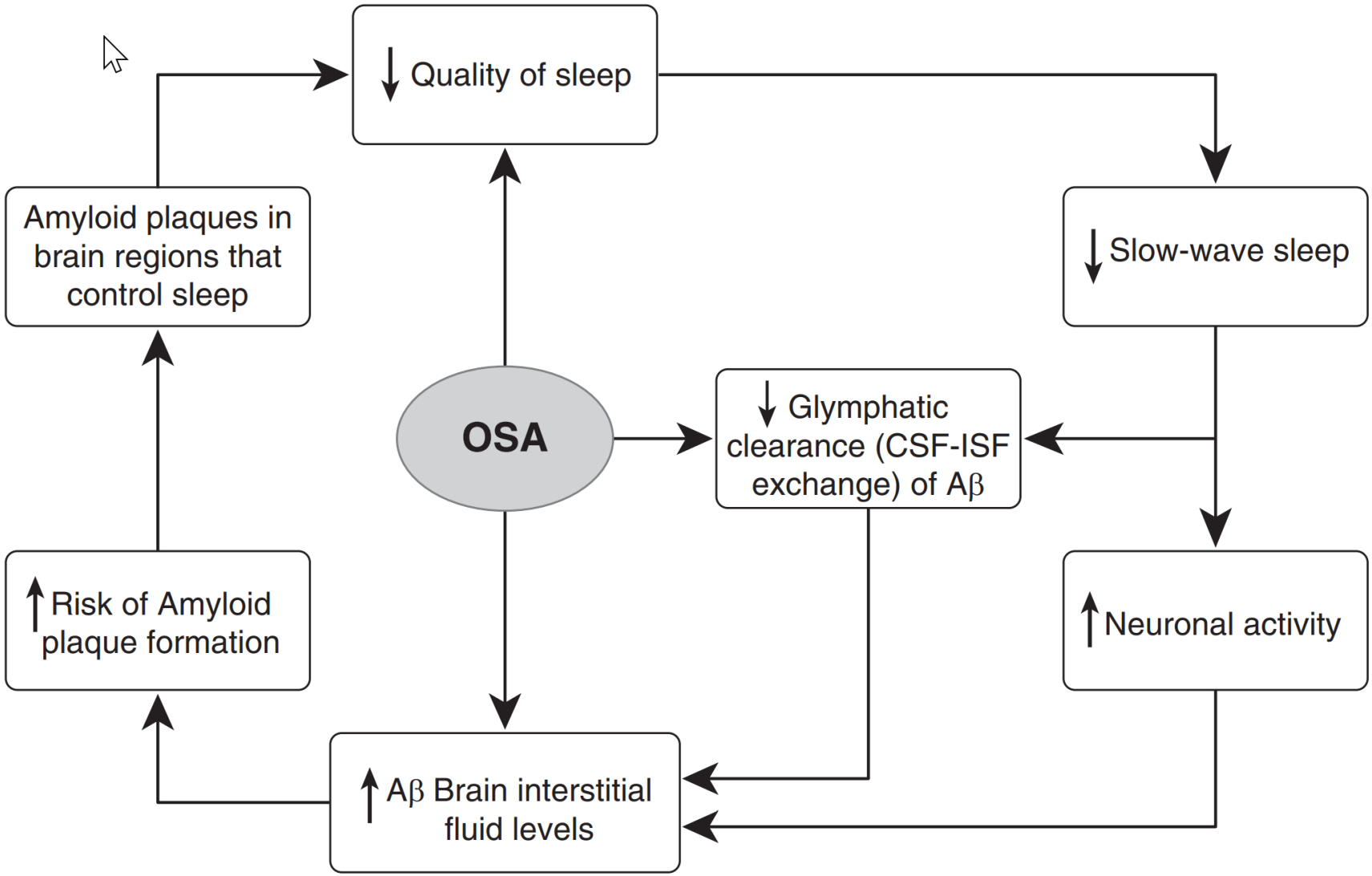
https://doi.org/10.1016/j.smrv.2018.08.001

Potential Mechanisms linking OSA to the Development of Dementia



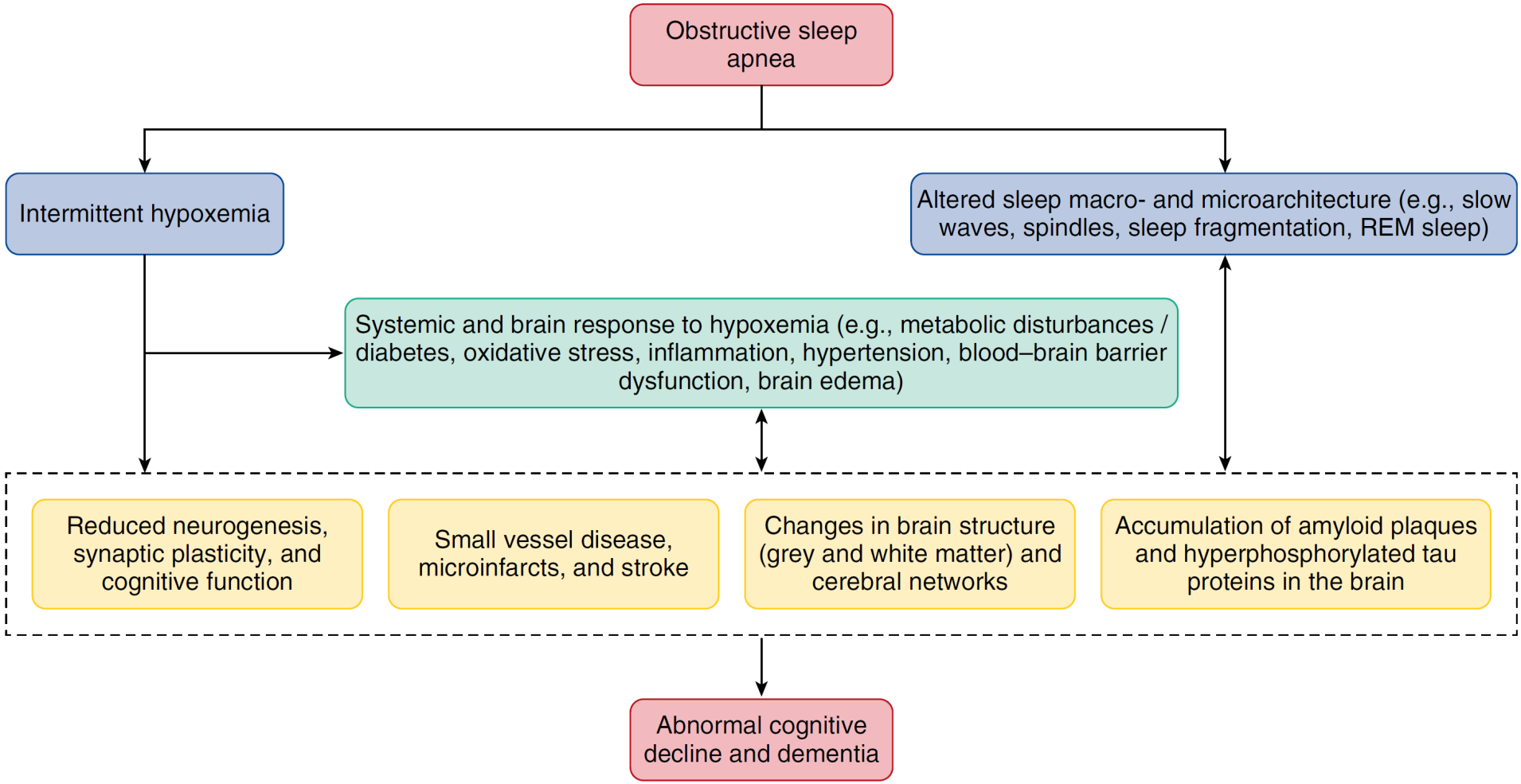
https://doi.org/10.1016/j.smrv.2018.08.001

OSA–related arousals and amyloid deposition



DOI: 10.1164/rccm.201704-0704OC

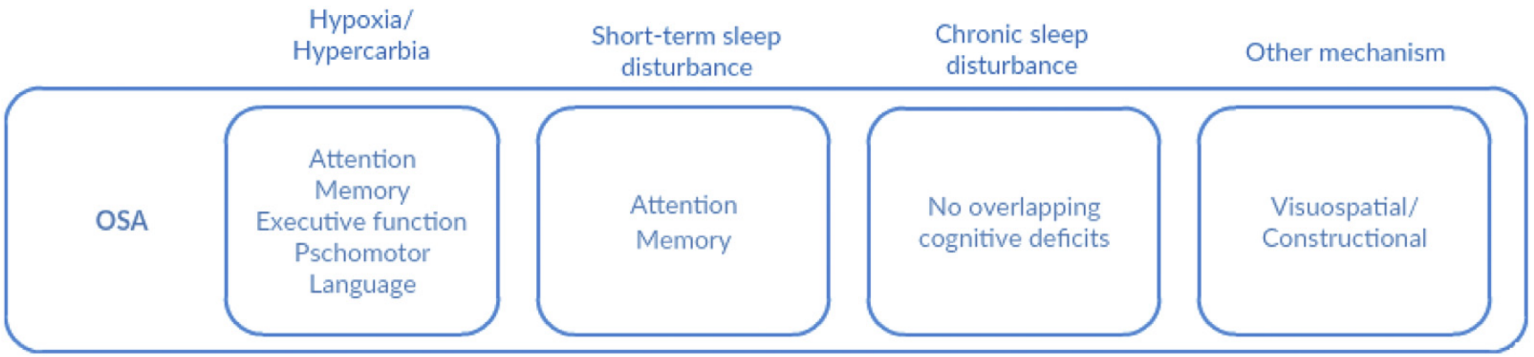
Schematic representation of possible mechanisms linking obstructive sleep apnea to dementia



http://dx.doi.org/10.1164/rccm.201801-0204PP

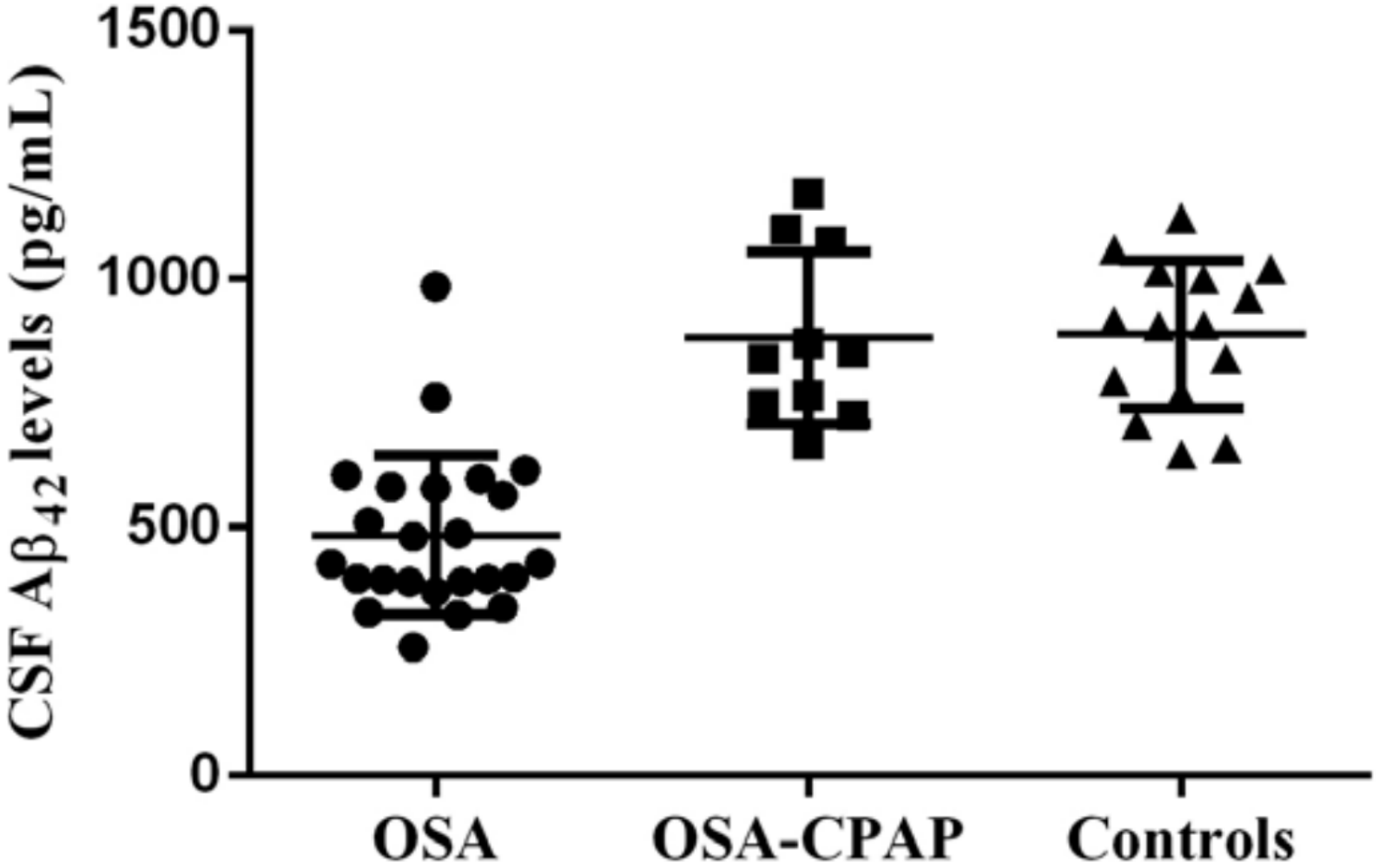
Cognitive Deficit in OSA

Condition	Attention	Memory	EF	WM	PsyM	VisSpat	Lang	General
OSA	YES	YES	YES	NO	YES	YES	YES	NO
COPD	YES	YES	YES	NO	YES	NO	YES	NO
Insomnia (long-term)	NO	NO	NO	NO	NO	NO	NO	NO
Sleep deprivation (short-term)	YES	YES	NO	NO	NO	NO	NO	YES



http://dx.doi.org/10.1016/j.smrv.2017.03.005

CPAP: AD-CSF biomarker

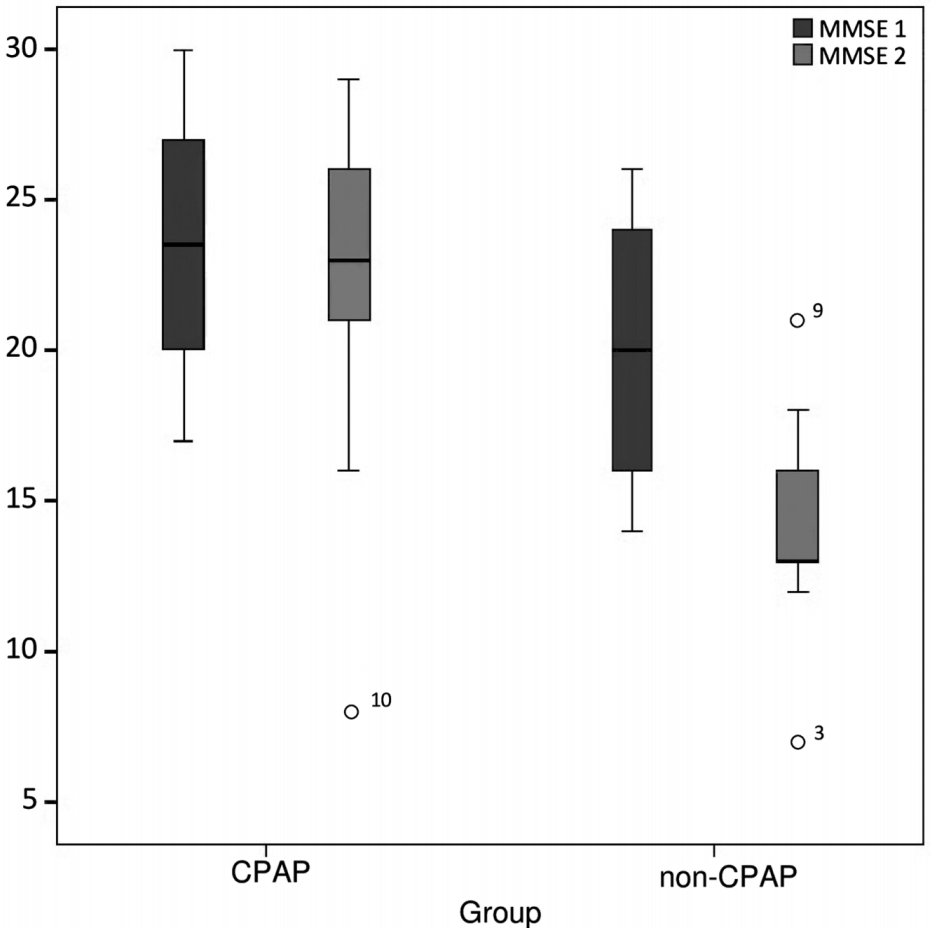


Liguori C, Sleep 2017;40(5).http://refhub.elsevier.com/S1087-0792(18)30038-8/sref63

CPAP and AD

Table 1 Baseline characteristics of the patients (n=23)

	CPAP+ (n=14)	CPAP− (n=9)	p Value
Age (years)*	73.4 (68; 79.6)	77.6 (74.8; 79.4)	0.17
Gender ratio H/F	10/4	4/5	0.38
Educational level (0/1)	6/8 (42.9%/57.1%)	7/2 (77.8%/22.2%)	0.19
MMSE at baseline*	23.5 (20; 27)	20 (16; 24)	0.09
AHI*	47.7 (36.7; 62.6)	43.3 (37.2; 51.2)	0.52
BMI (kg/m^2)*	26.7 (24.7; 28.3)	24.5 (23.0; 33.1)	0.81
Vascular risk factor (at least 1)	10 (71.4%)	7 (77.8%)	1
Hypertension	10 (71.4%)	7 (77.7%)	0.88
Diabetes	2 (14.3%)	3 (33.3%)	0.57
Dyslipidaemia	8 (57.1%)	6 (66.6%)	0.98
Smoking	10 (71.4%)	3 (33.3%)	0.17
Heart disease	9 (20.5%)	3 (33.3%)	0.3
Antihypertensive drugs	8 (57.1%)	7 (77.8%)	0.39
Statin	6 (42.9%)	5 (55.6%)	0.68
Antiplatelet agent	8 (57.1%)	5 (55.6%)	1
Cholinesterase inhibitor	13 (92.8%)	9 (100%)	0.81
Memantine	9 (64.2%)	8 (88%)	0.40
Duration of follow-up (years)†	3.3 (1.8; 3.6)	3.0 (2.3; 3.6)	1



Troussière A-C, et al. J Neurol Neurosurg Psychiatry 2014;85:1405–1408. doi:10.1136/jnnp-2013-307544

OSA and Cognitive Function in the General Population

- Systematic reviews and meta-analyses have reported
  - Relatively consistent deficits in attention, vigilance and executive functions
  - Occasional impairment of some subdomains of memory
  - Relative sparing of visuospatial abilities, language abilities, psychomotor function, short-term memory, and global cognition.
- Apart from attention and vigilance, more severe OSA did not produce a greater impact on other cognitive domains as compared with milder OSA

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Beebe DW.. Sleep **2003**, 26, 298–307.
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OSA and Dementia

- Older individuals with OSA at baseline were more likely to develop cognitive impairment and, subsequently, evolve towards frank dementia at follow up.
- Amongst elderly women, the presence of OSA was associated with increased odds of developing subsequent mild cognitive impairment (MCI) and dementia (OR: 1.85; 95% CI: 1.11 to 3.08)
- Patients with sleep disordered breathing developed MCI or AD-related dementia about 10 years earlier than patients without OSA.
- Severe OSA was associated with an increased risk of all-cause and AD-related dementia
- AD patients had five times the odds of OSA as compared with healthy controls and it was estimated that OSA occurred in nearly 50% of AD patients

Yae K. JAMA J. Am. Med. Assoc. **2011**, 306, 613–619. Chang WP. PLoS ONE **2013**, 8, e78655.
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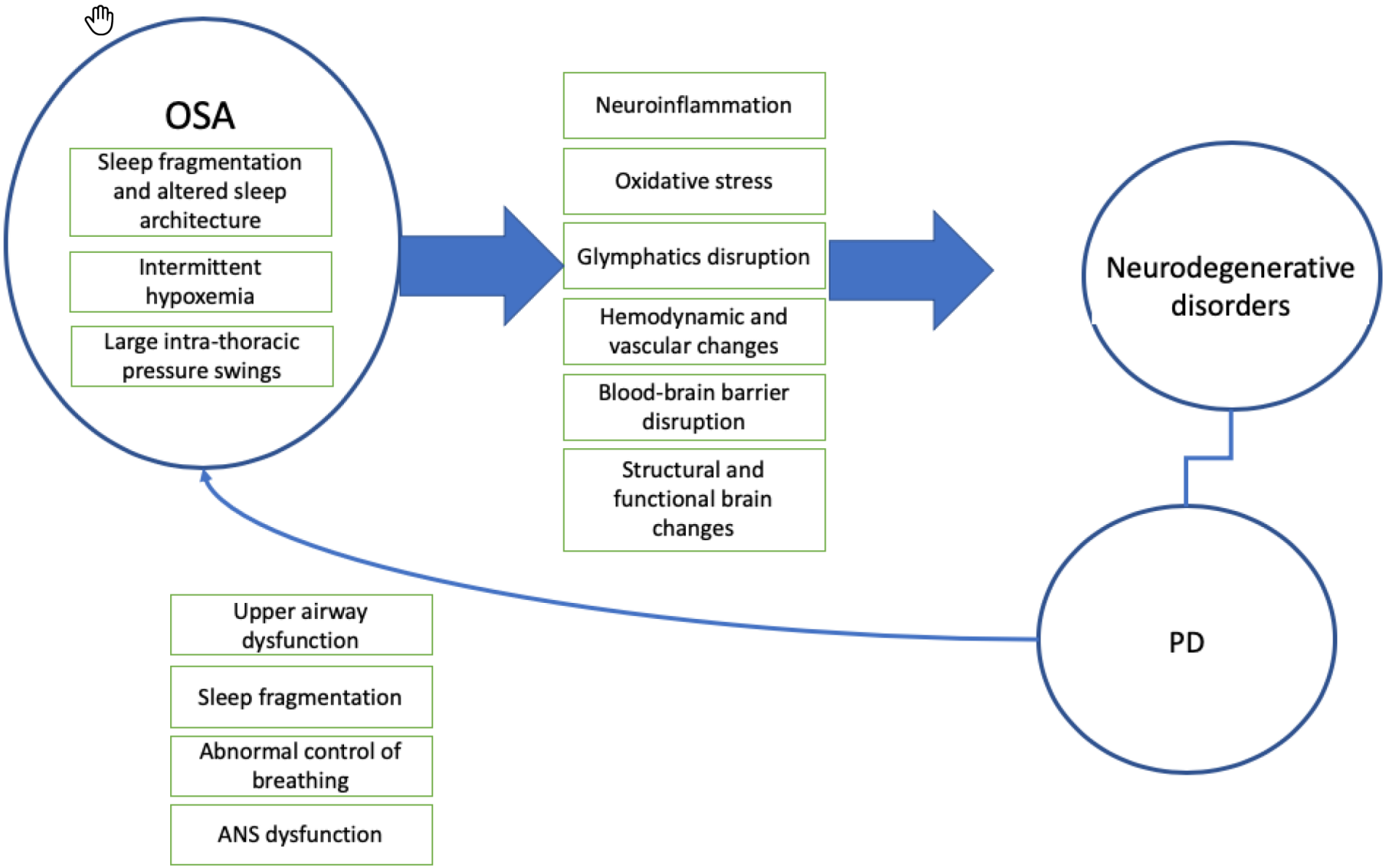
Pathogenesis of Cognitive Impairment in OSA



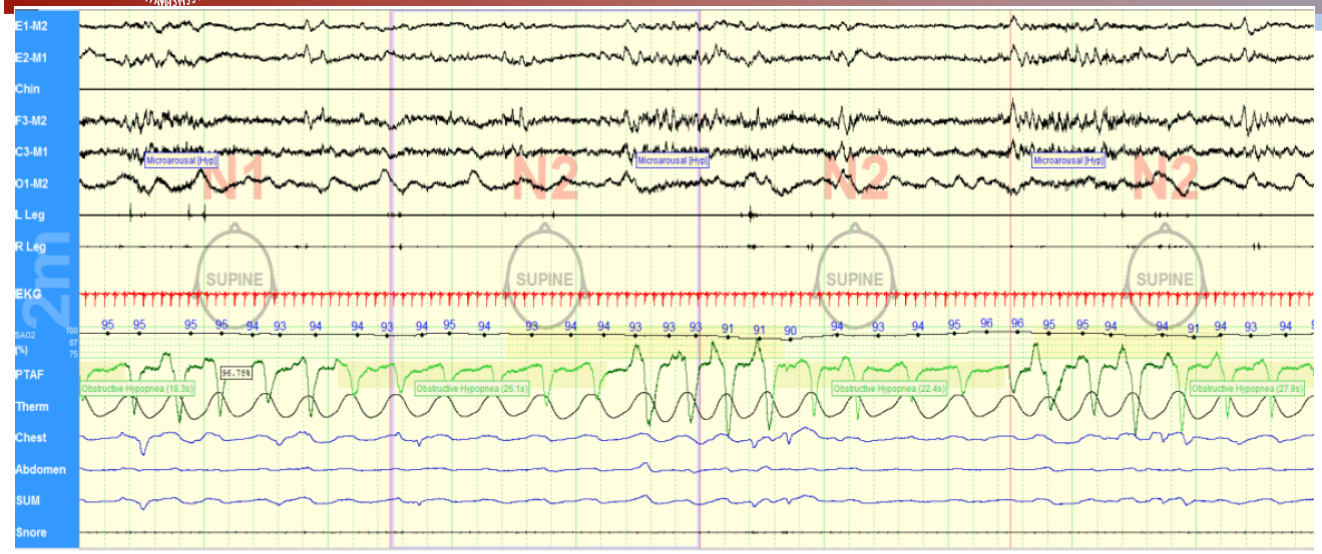
http://dx.doi.org/10.3390/jcm9020297

OSA and PD

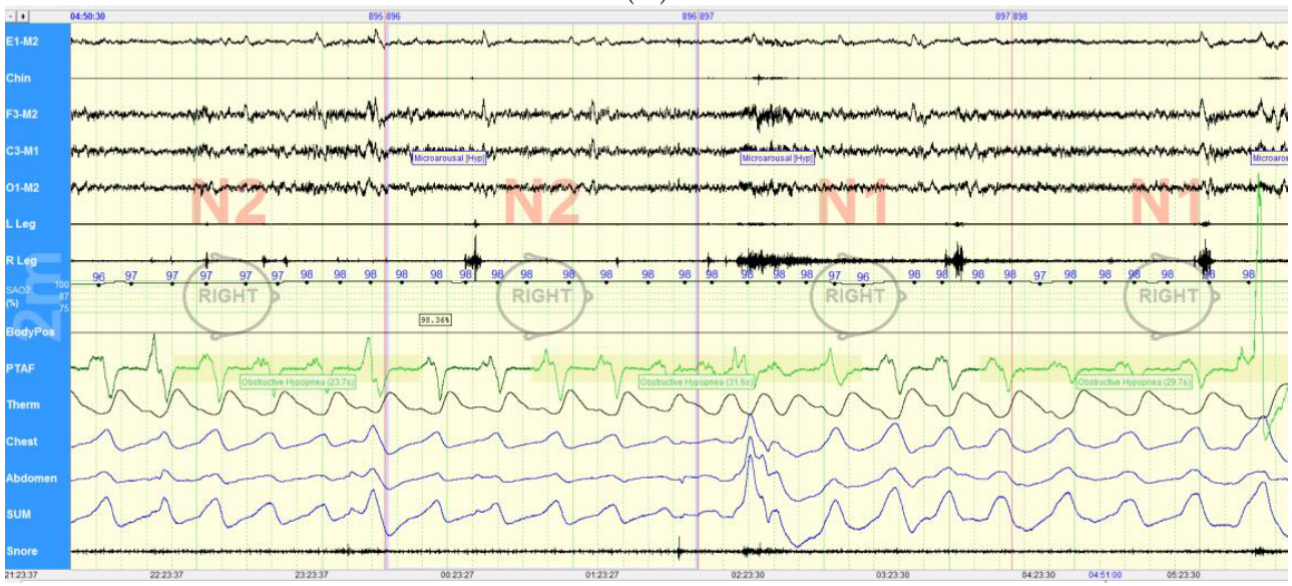
- Cognitive dysfunction, measured using the MoCA, was greater in PD patients with concomitant OSA and that the impairment increased with OSA severity.
- PD patients with OSA had significantly higher baseline motor MDS-UPDRS.
- Patients with OSA treated with CPAP showed a stabilization of their motor MDS-UPDRS scores over a 12-month follow-up period.

Cochen De CV. Sleep Med. 2010, 11, 247–252.
Meng L. Parkinsonism Relat. Disord. 2019, 70, 45–50.

Patterns of upper airway obstruction in Parkinson's disease.



(A)



(B)

(**A**) Obstructive hypopnea

(**B**) Upper airway instability

http://dx.doi.org/10.3390/jcm9020297

Rapid eye movement (REM) sleep behavior disorder (RBD)

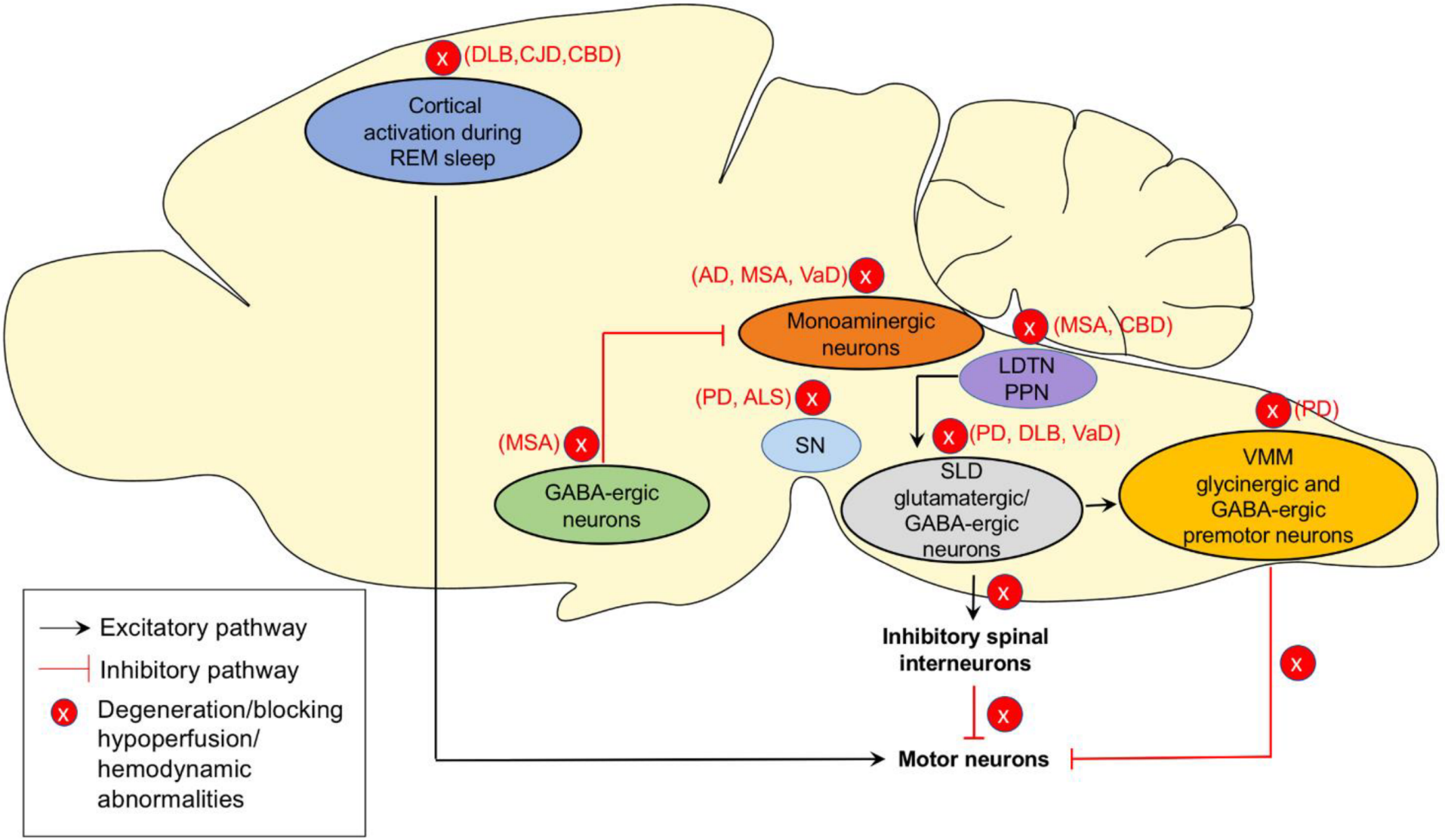
- Characterized by dream enactment and loss of muscle atonia during REM sleep.
- Generally chronic, progressive
- Usually affects 0.5% of the general population aged over 50 years and 7% of people aged over 70 years.
- Males had more aggressive RBD than females.
- Idiopathic RBD (iRBD) refers to RBD in the absence of other neurological diseases, whereas symptomatic RBD is secondary to neurological diseases and medication

Summarized prevalence, gender difference and underlying mechanisms of RBD in neurodegenerative diseases

Disease	Prevalence	Gender difference	Possible mechanisms of pathogenesis of RBD
PD	42.3%[50]	Male>female [51]	α-syn pathology affects the circuit that regulates REM sleep, associated with *GBA* [39], *SCARB2* [40], *MAPT* [40], *USP25*[40], *PINK1* [41], *LRRK2* [2] mutations
MSA	88%[33]	Female>male [59]	α-syn pathology affects the circuit that regulates REM sleep, depletion of cholinergic neurons in the PPN/LDTN complex, periaqueductal grey matter, and LC [33]
PSP	13%[13]	-	Loss of cholinergic neurons in the pedunculopontine tegmentum [13]
CBD	Case reports[38, 68]	2 female patients [38, 68]	Degenerative process in cortical and subcortical structures and in the nuclei of the brain stem and pedunculopontine pathways [38].
AD	4.8-26.7%[12, 71]	Male>female [12]	An imbalance of neurotransmitter acetylcholine [12], neuronal loss in LC [12]
DLB	46.7-83%[81-83]	Male>female [82]	α-syn pathology affects the circuit that regulates REM sleep [4]
FTD	Rare (only case report)[90]	1 male patient [90]	Associated with C9ORF72 repeat expansion [89]
VaD	25.6%-72.6%[81, 93]	-	Hypoperfusion or hemodynamic abnormalities affect the brain areas that regulate REM sleep [4]
HD	12% or lower[14, 96]	Female>male [14]	Associated with mutant huntingtin [14]
ALS	4.9%[15]	2 male patients [15]	Neurodegeneration of nuclei in REM-associated pathways in the brainstem and the dysfunction of dopaminergic system in substantia nigra striatum may be the main pathophysiological culprit in the development of RBD [15], associated with C9ORF72 repeat expansion [91, 100]
CJD	7.1%[101]	2 male patients [101]	Associated with corticothalamic degeneration [102]

Zhang Feng, Aging and disease, 2020, 11(2): 315-326.

Potential mechanisms of RBD and related pathological pathways



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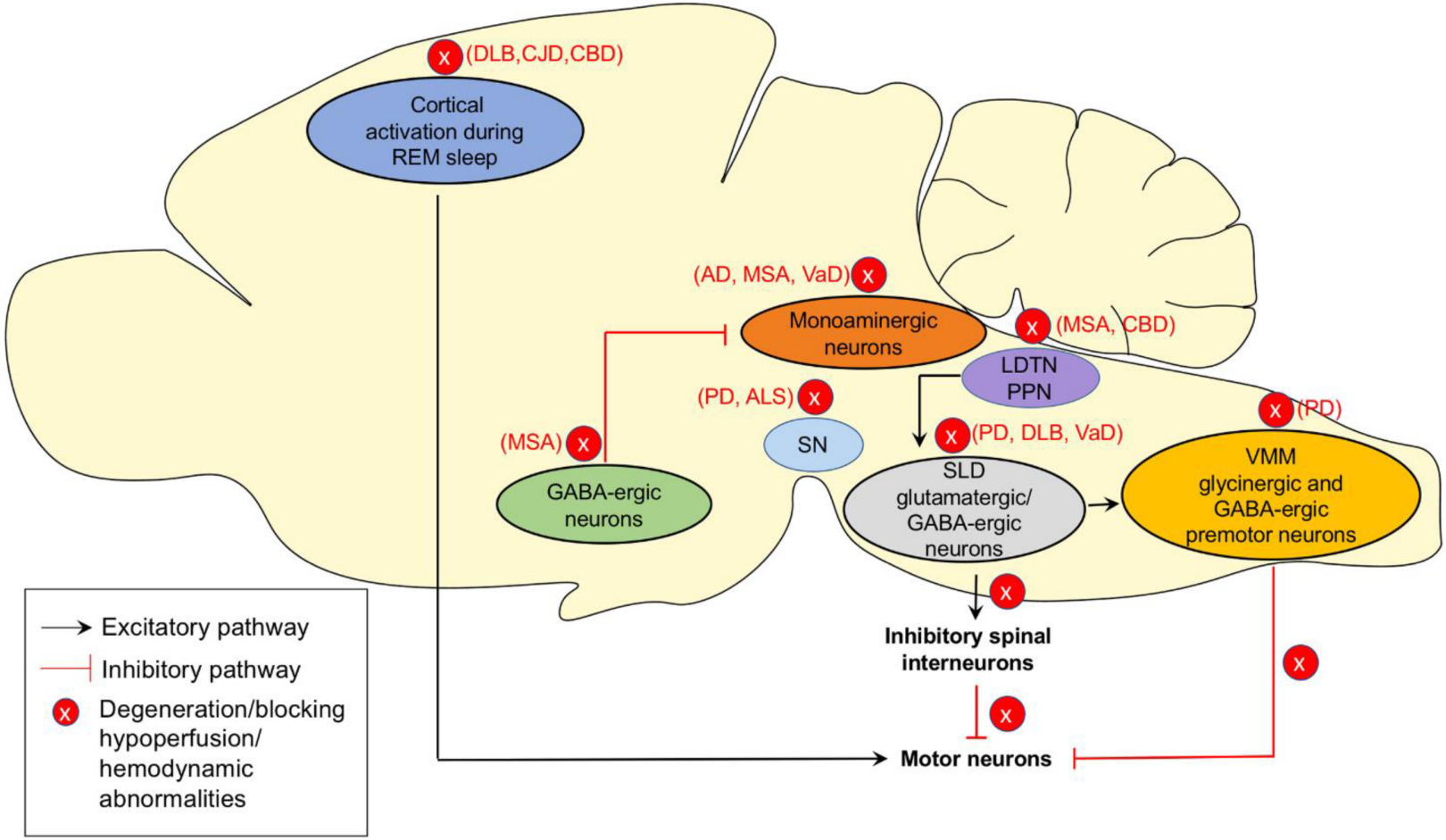

The γ-aminobutyric acid (GABA)-ergic neurons located in the lateral hypothalamus and other nuclei inactivate REM-inhibiting monoaminergic neurons in the tuberomammillary nucleus, locus coeruleus (LC), and dorsal raphe and GABA-ergic neurons in the ventrolateral periaqueductal grey (vlPAG) to induce REM sleep. Sublaterodorsal nucleus (SLD) glutamatergic/GABA-ergic neurons stimulate inhibitory spinal interneurons or glycinergic and GABA-ergic premotor neurons in the ventromedial medulla (VMM) resulting in skeletal muscle atonia. SLD neurons may be activated by the cholinergic laterodorsal tegmental nucleus and pedunculopontine tegmental nucleus (LDTN/PPN) neurons. The cortical activation during REM sleep leads to the activation of spinal motor neurons. Blocking glycine and GABA receptors or the degeneration of glycinergic and GABA-ergic neurons in the SLD and VMM removes the inhibition of spinal motor neurons and prevents the induction of muscle atonia. This could be the possible mechanism of RBD. In neurodegenerative diseases, pathological changes affecting the REM sleep regulating nuclei and circuits may contribute to the pathogenesis of RBD in these specific diseases.

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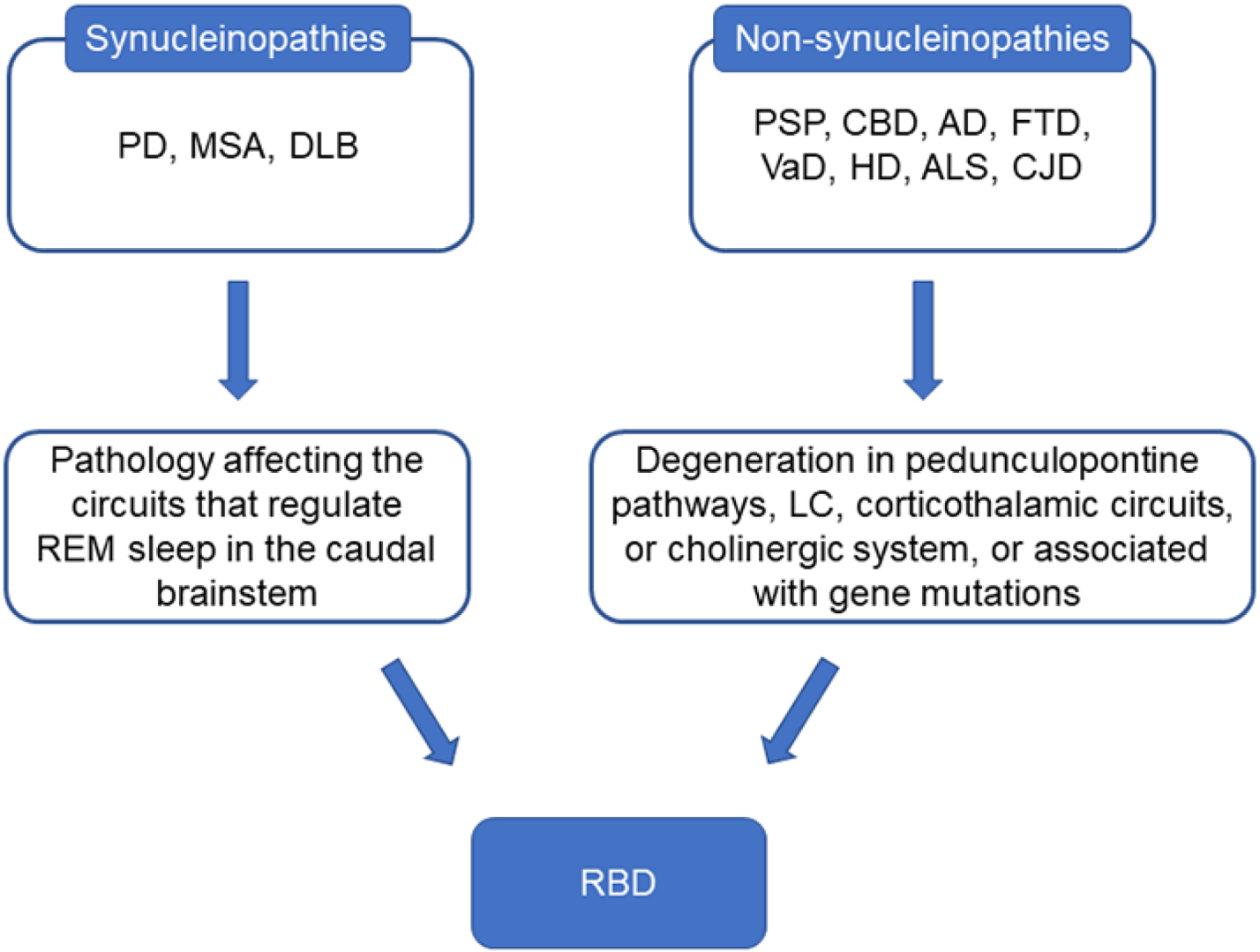
The possible mechanisms of RBD



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Summarized prevalence, gender difference and underlying mechanisms of RBD in neurodegenerative diseases.

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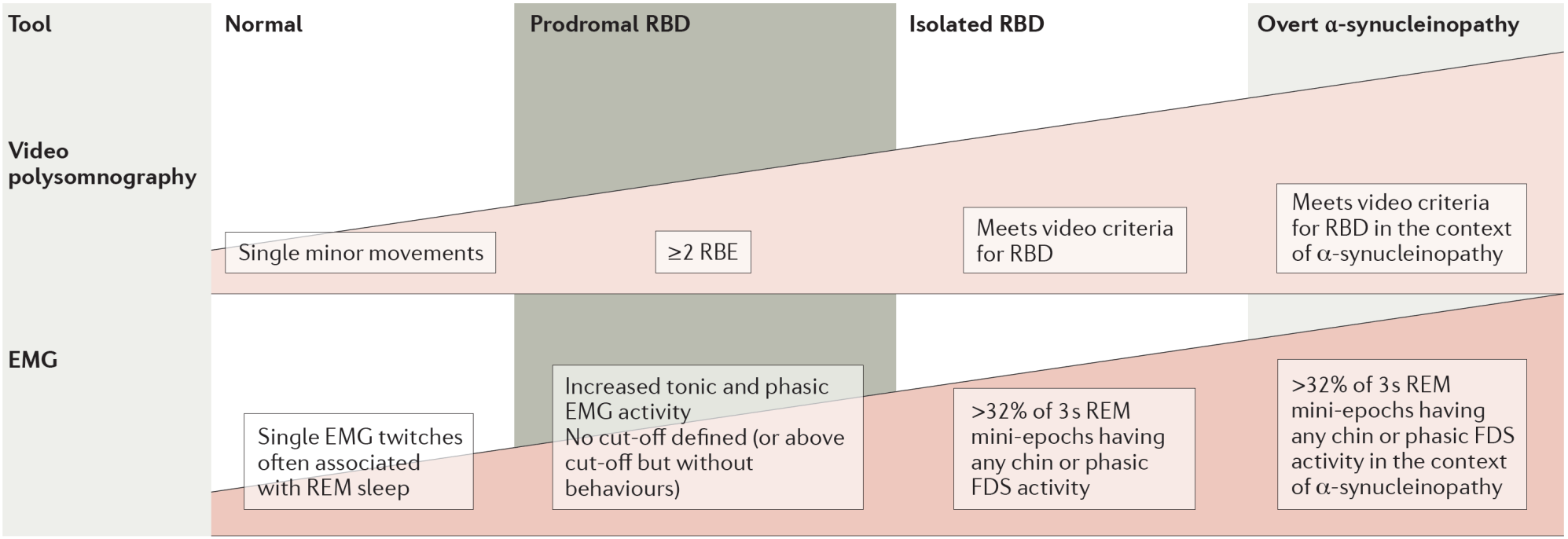
The new concept of prodromal RBD



doi:10.1038/nrneurol.2017.157

Biomarkers of in RBD

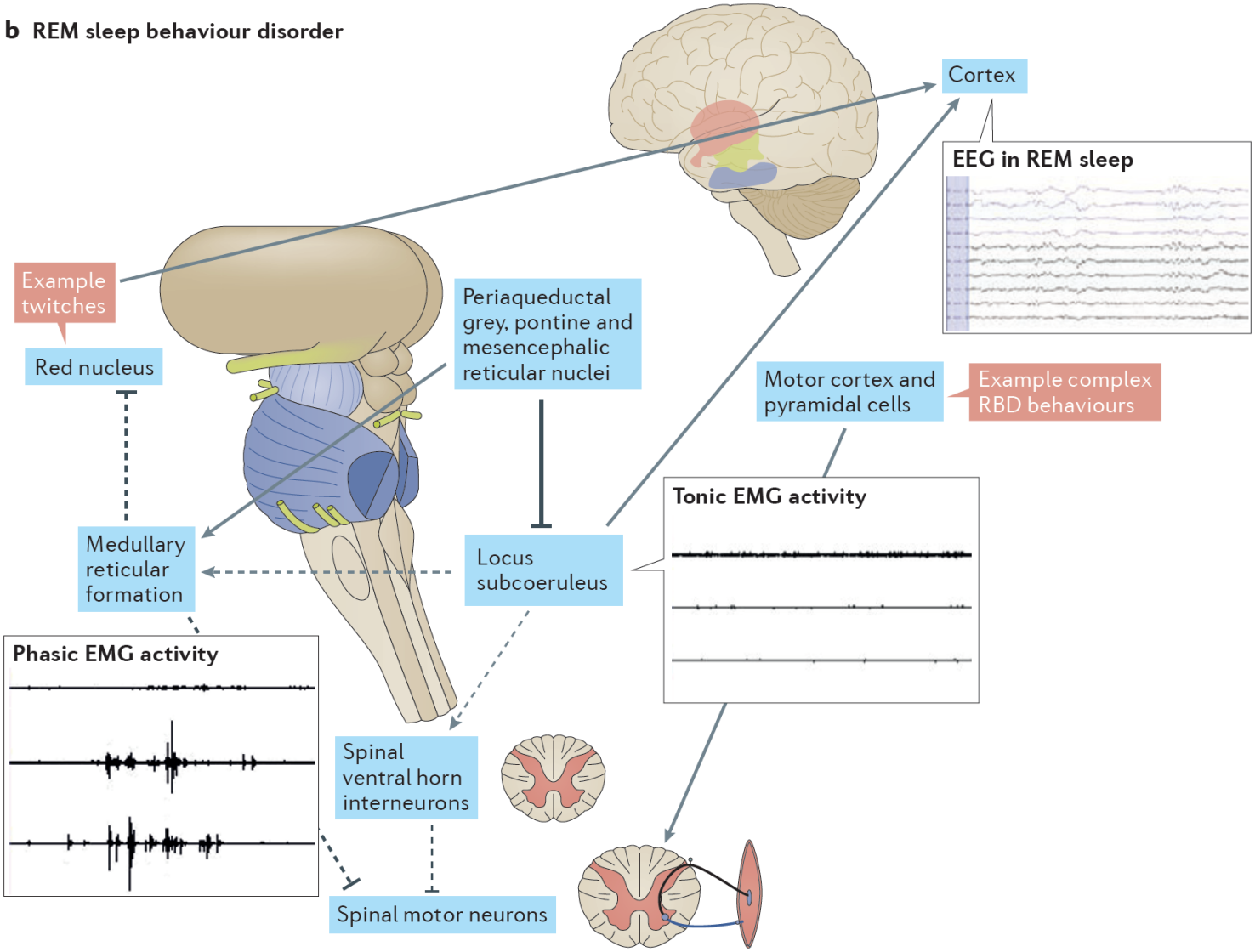
- Brain imaging
  - MRI brain, Midbrain transcranial ultrasonography, DATimaging, Cerebral perfusion and metabolic imaging.

- Physiological biomarkers
  - Olfactory function, autonomic function, EEG findings, Neuropsychological assessment

- **Key video-polysomnography biomarkers**

doi:10.1038/nrneurol.2017.157

Key Video-polysomnography Biomarkers



doi:10.1038/nrneurol.2017.157

Approach to the patients with sleep problems

Sleep History

- Identify the symptom (onset, duration, pattern, and severity)
- Evaluate 24-hour sleep/wakefulness patterns
- Review 1- to 2-week caregiver sleep diary
- Apply appropriate sleep studies (PSG, actigraphy, etc.)

Sleep diary

ศูนย์นิทรรักษ์ศิริราช

บันทึกการนอนหลับ

ชื่อ ___________________________

HN.___________________________

1. ใส่เครื่องหมาย ↓ ทุกครั้งที่เข้าที่นอน
2. ใส่เครื่องหมาย ↑ ทุกครั้งที่ลุกออกจากที่นอน
3. ระบายสีดำ ▒ ช่วงเวลาที่นอนหลับ

วัน	วันที่	24:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	22:00	23:00	24:00
จันทร์	1 มี.ค.								↑												↓					
อังคาร	2 เม.ย.									↑					↓	↑								↓		

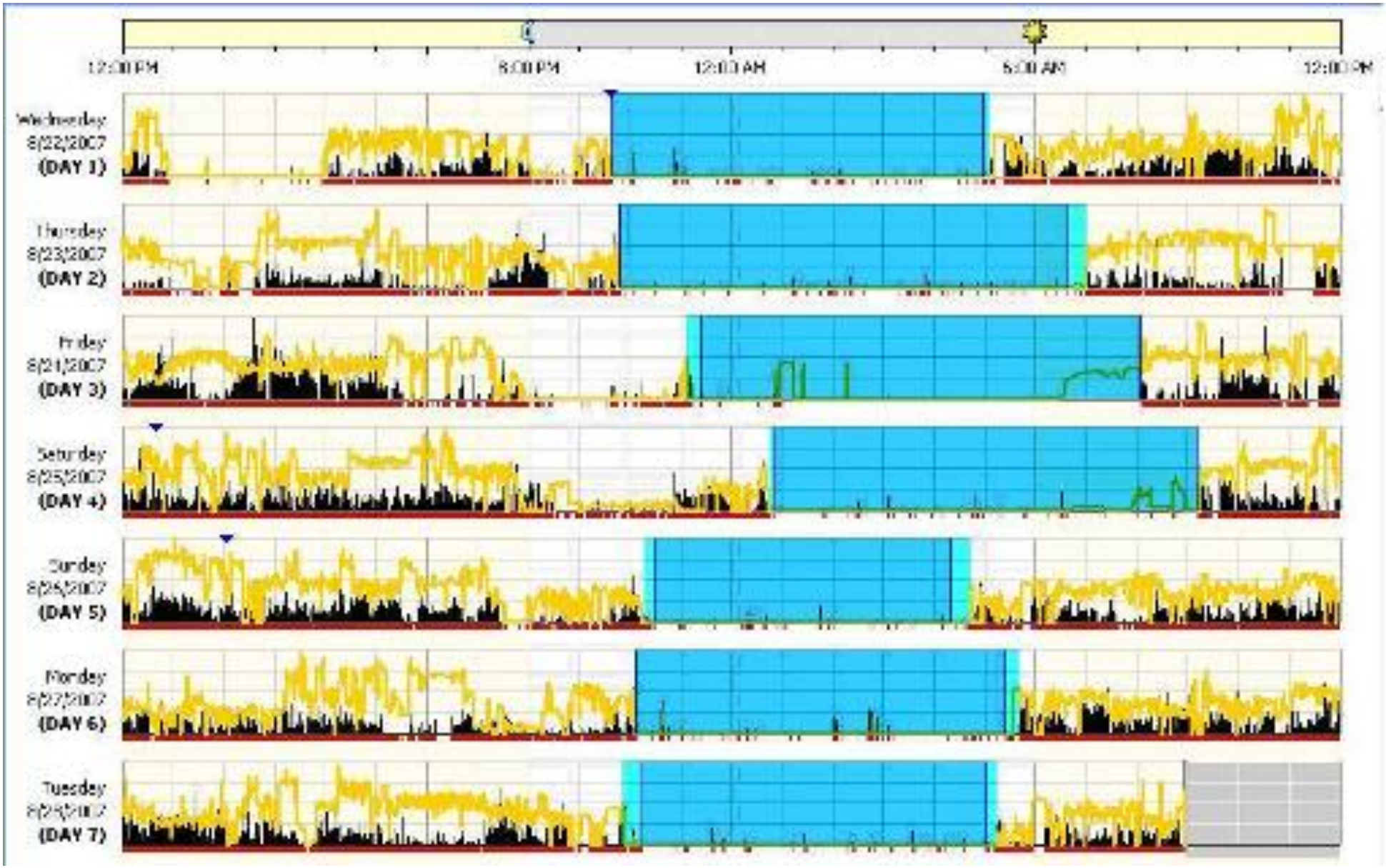
Polysomnography

Wrist Actigraphy

- **Quantify inactivity versus activity, or sleep versus wake for consecutive 24-h periods, appears as an alternative, less intrusive and equally reliable, procedure**

1) Significant correlation between EEG recording and actigraphy for total sleep and wake time
2) High sensitivity (87%, ability to detect wake) and specificity (90%, ability to detect sleep) of actigraphy, compared to behavioral observations

Wrist Actigraphy


8:00 PM
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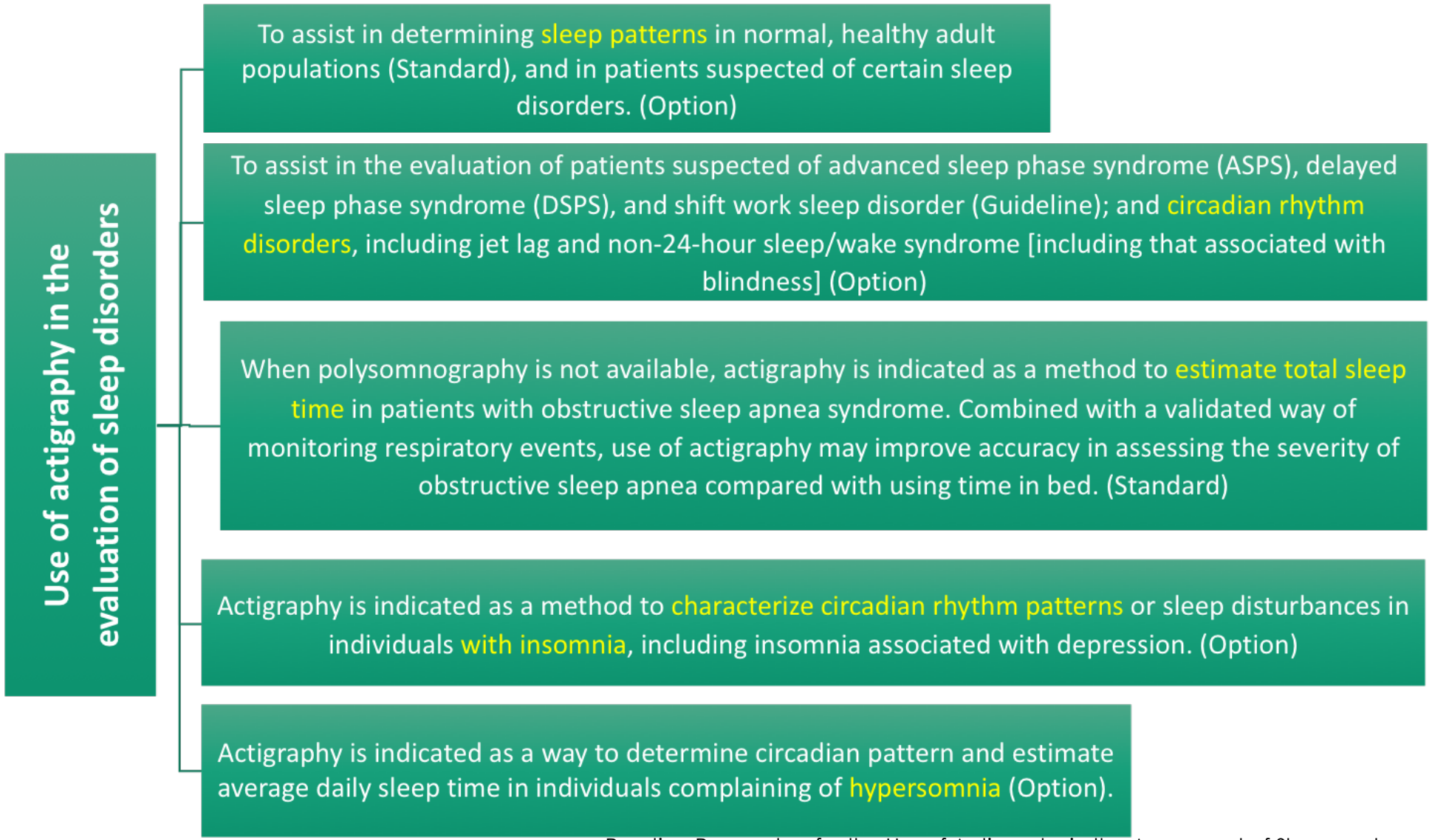
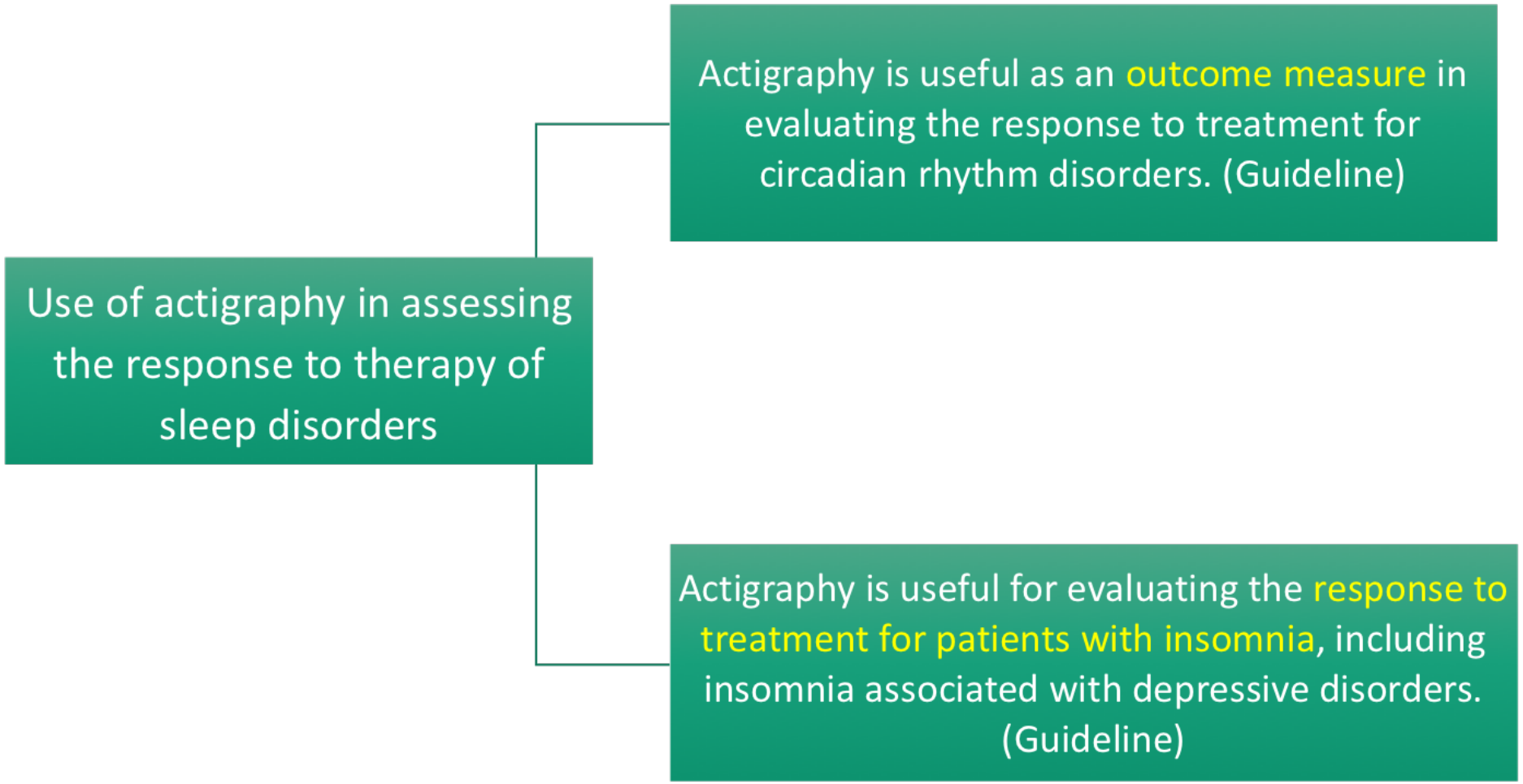
(DAY 7)

Actigraphy



Practice Parameters for the Use of Actigraphy in the Assessment of Sleep and Sleep Disorders: An Update for 2007 , *SLEEP, Vol. 30, No. 4, 2007*

Actigraphy



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