

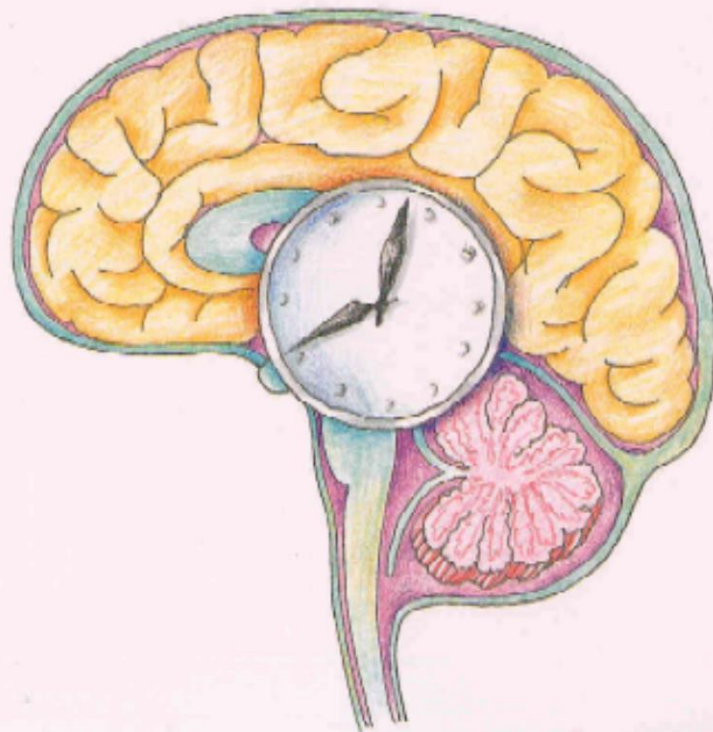
# Sömnrubbningar vid Parkinsons sjukdom

**Lena Leissner**

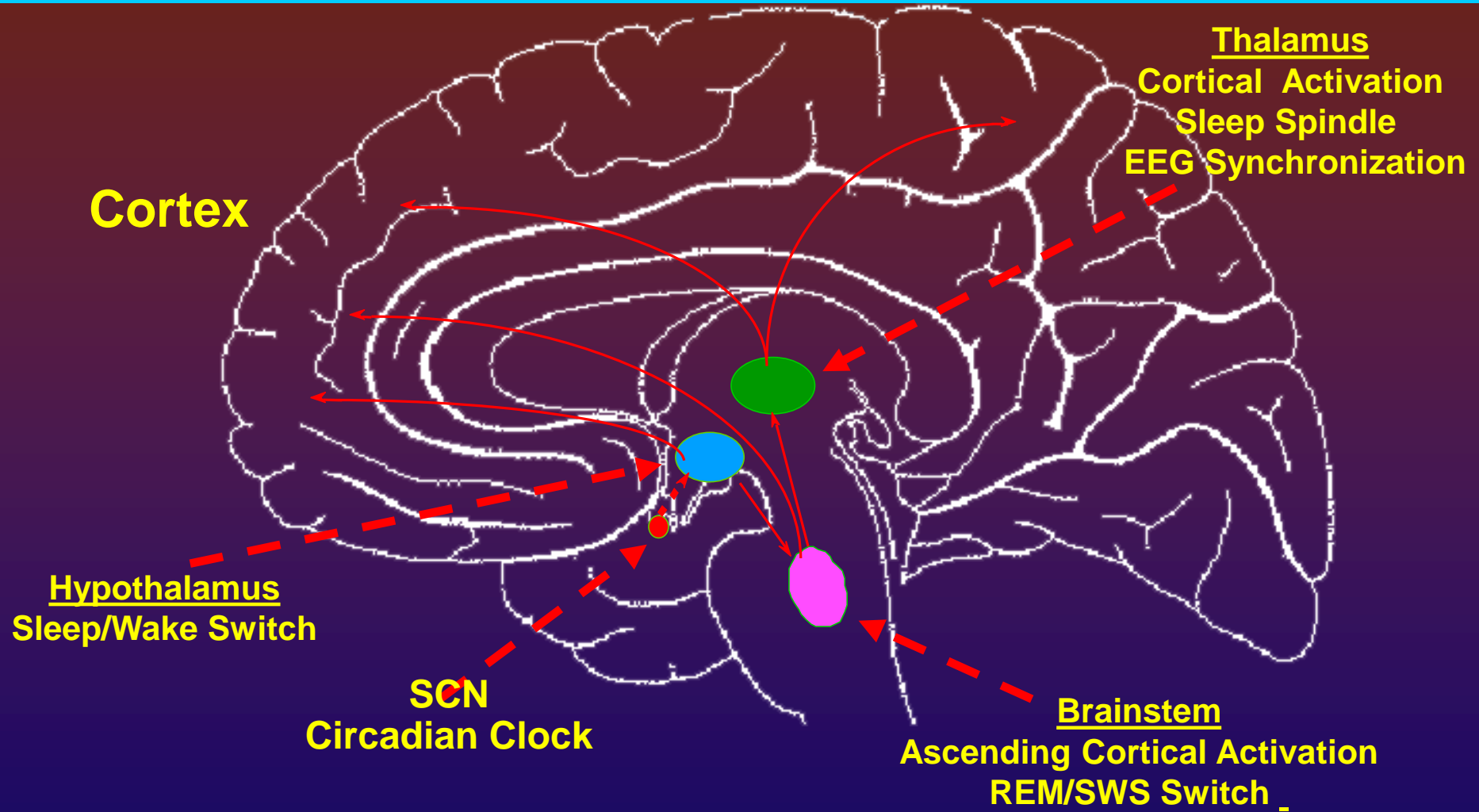
**Sömnenheten Neurokliniken**

**Universitetssjukhuset Örebro**

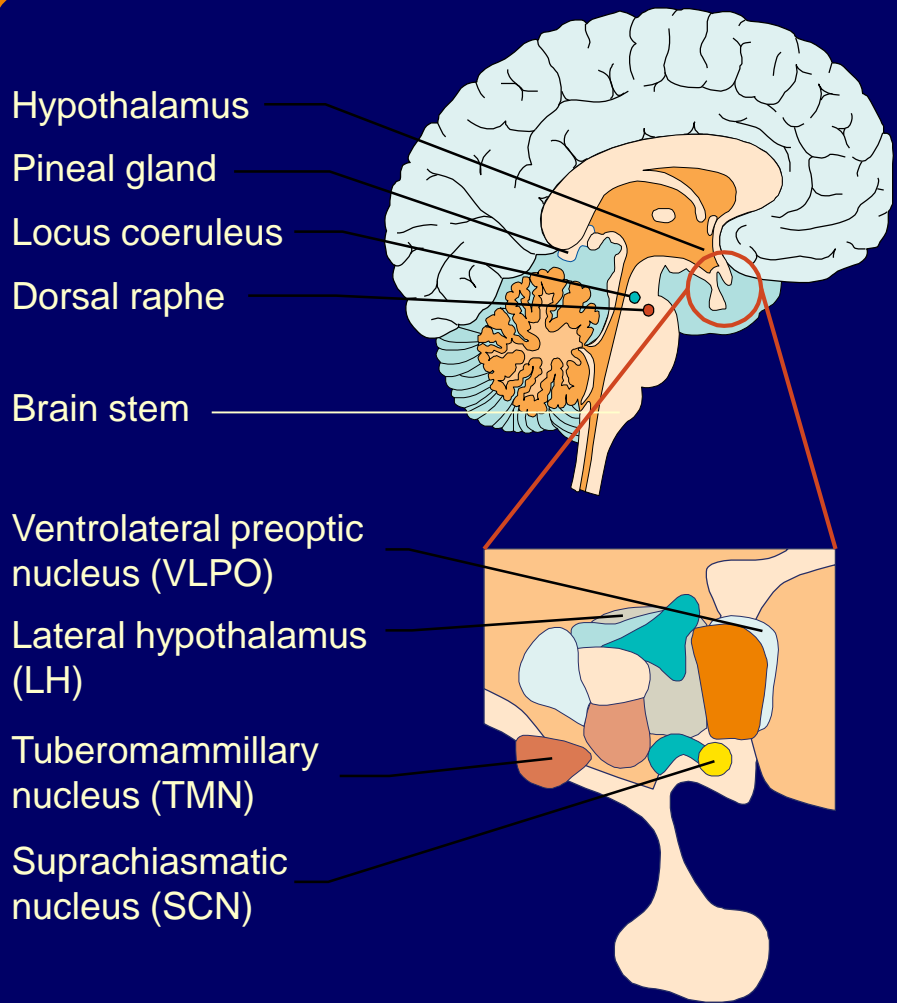
# SÖMNMEN PÅVERKAS AV YTTRE OCH INRE FAKTORER



# Sleep: Neurophysiology



# Brain regions coordinating the sleep–wake cycle



- ❖ Arousal-promoting regions
  - ❖ SCN
  - ❖ LH
  - ❖ TMN
- ❖ Sleep-promoting regions
  - ❖ VLPO
  - ❖ Pineal gland
- ❖ Brain stem



# Signalsubstanser

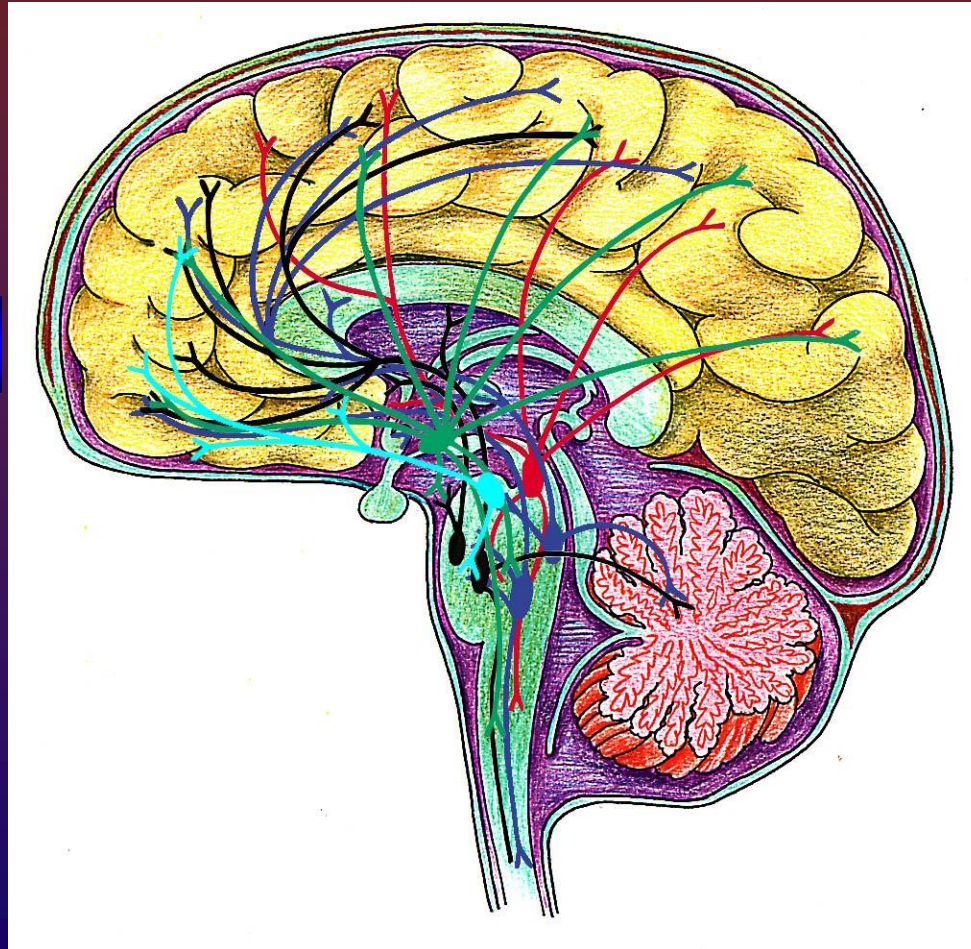
Dopamin

Noradrenalin

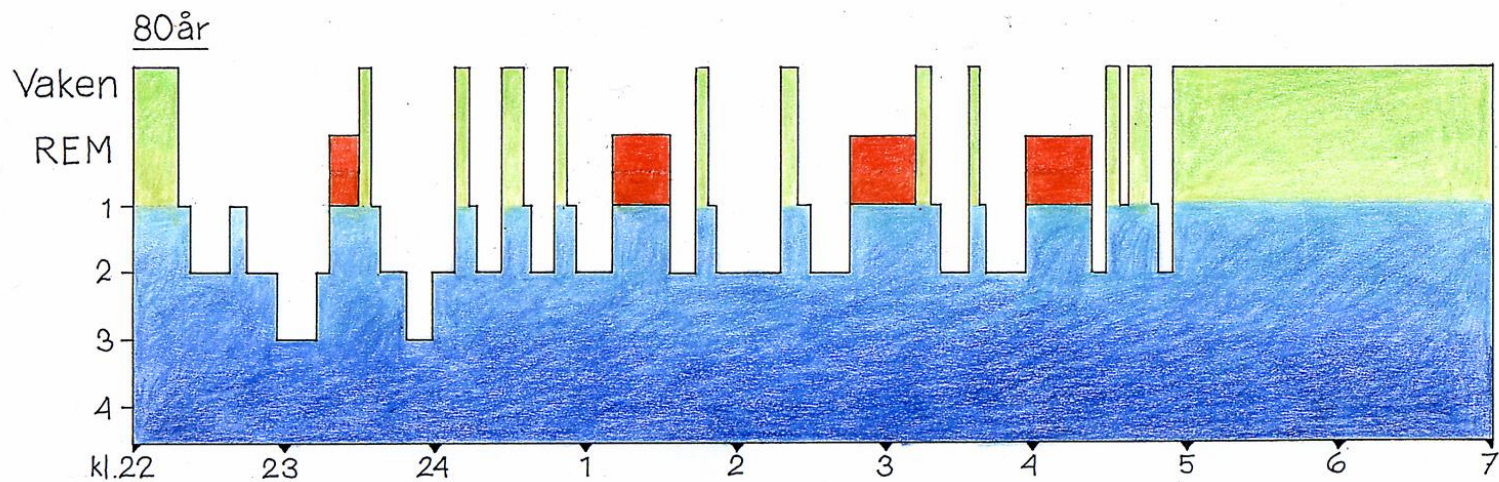
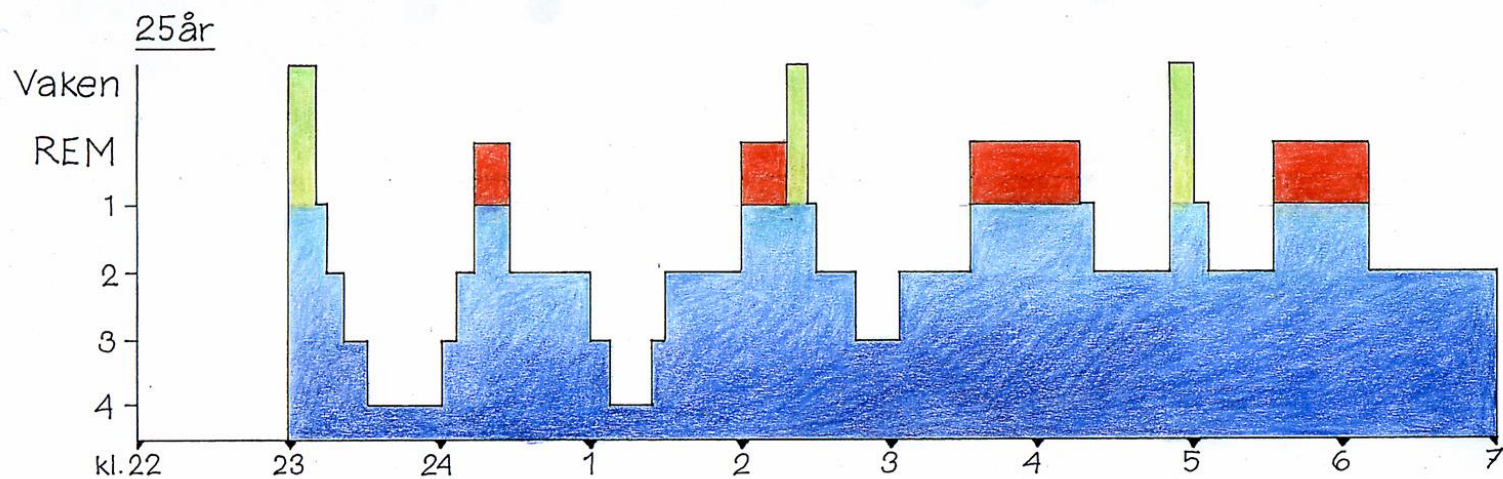
Serotonin

Acetylkinolin

Hypocretin



# Sömmönster





# KLASSIFIKATION AV STÖRNINGAR I SÖMN- VAKENHETSMÖNSTRET

## 1. Insomnier

Sömnlöshet, svårt att somna och/eller svårt att bibehålla sömn.

## 2. Hypersomnier

Uttalad sömnighet och/eller trötthet på dagen, trots god nattsömn.

## 3. Störningar i sömn-vakenhetsrytmen

Skiftarbete

Jet-lag

Icke 24-timmars dygn

Försenad sömnfas

## 4. Parasomnier

Göra "ovidkommande" saker under sömn t ex

Gå i sömnen

Tala i sömnen

Gnissla tänder

Kissa på sig

Nattskräck

PLM



# Trötthet vid Parkinsons sjukdom

1. **Insomnier** på grund av  
PD i sig  
farmaka  
sömnsjukdom  
depression  
dygnsrytmeffekter

2. **Hypersomnier** på grund av  
PD i sig  
farmaka  
sömnsjukdom  
depression  
dygnsrytmeffekter

3. **Förändrad drömsömn**  
hypnagoga hallucinationer  
RSBD (Rem Sleep Behaviour Disorder)





RLS

Restless Legs Syndrome

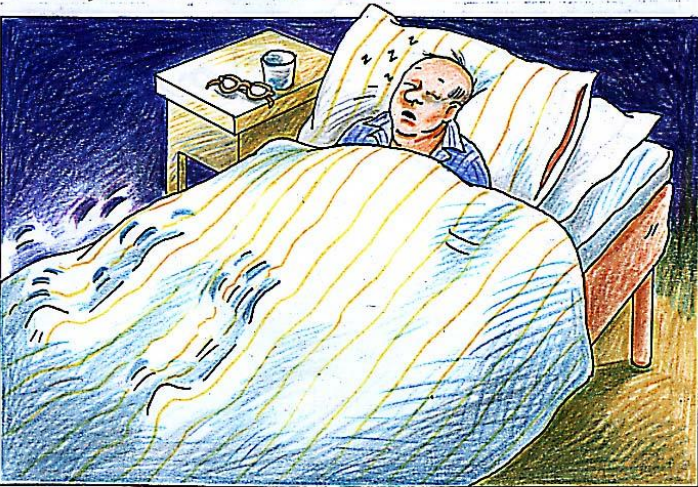
Ekboms's Disease

The Swedish Disease

WED

Willis-Ekboms Disease

# RLS och PLMS



## Restless legs - RLS

Prevalens:

5-15%

20-40% vid PD

## Periodiska benrörelser under sömn - PLMS

Prevalens:

>80% av RLS-patienter

>35% av PD-patienter utan RLS



## Diagnostiska kriterier:

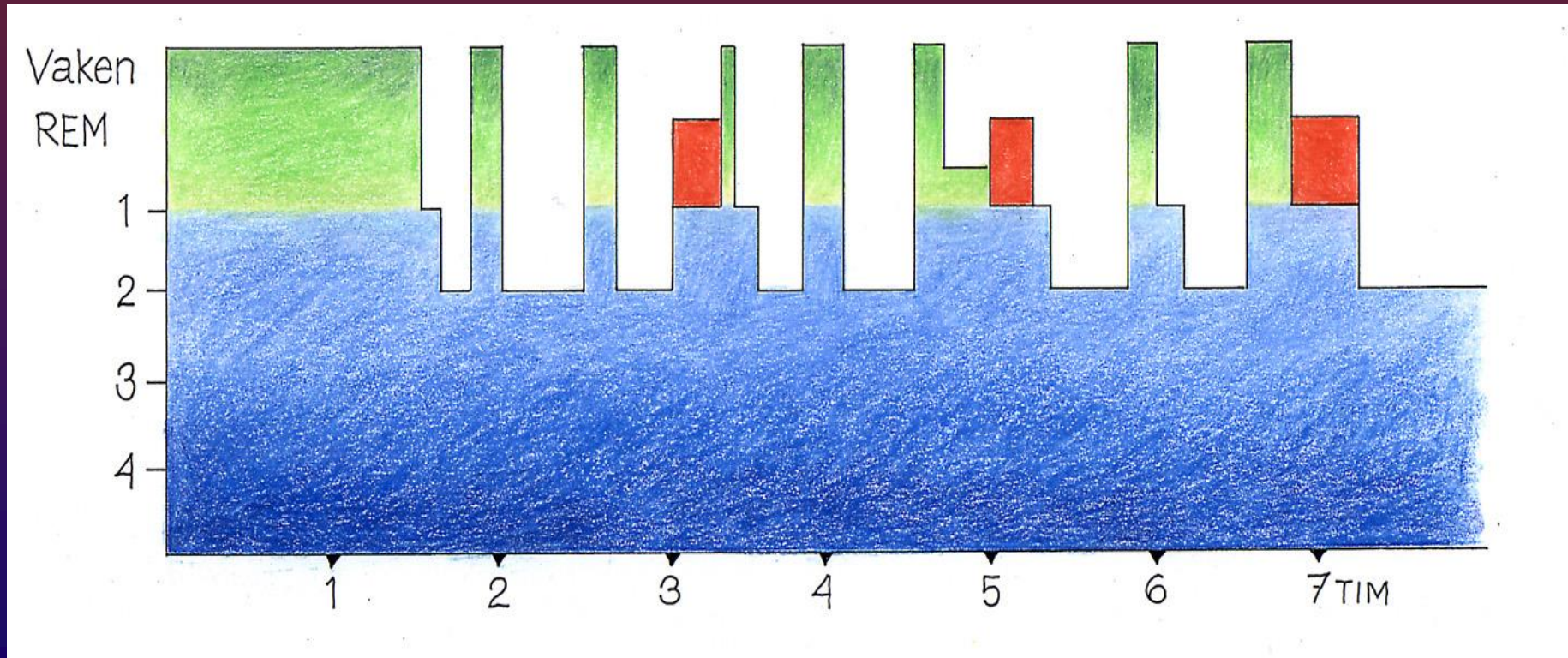
- ❖ 1: Obehagliga, ibland smärtsamma parestesier i extremiteterna, oftast i benen.
- ❖ 2: Symtomen uppträder i vila och lindras av aktivitet.
- ❖ 3: Symtomen medför ett obetvingligt behov av motorisk aktivitet.
- ❖ 4: Cirkadisk variation föreligger med aggraverade symtom kvälls- och nattetid.



# Parestesier ja, men vad säger patienten?

- ❖ Domningar
- ❖ Stickningar
- ❖ Kramper
- ❖ Värk
- ❖ Klåda
- ❖ Sveda
- ❖ Hettningar
- ❖ Oro
- ❖ Svaghet
- ❖ Sockerdricks känsla
- ❖ Krypningar
- ❖ Dragningar
- ❖ Pulsationer
- ❖ Bränningar
- ”Maskar under skinnet”
- Obehag
- Rastlöshet
- Obalans
- Sprittningar
- Smärtor
- Knivhugg
- Köldvågor
- Överkänslighet
- Strömstötar
- Rinnande vatten
- Pirringar
- ”Borrmaskin”
- Durrningar

# Sömnmönster vid RLS/PLMS





# RLS

## ❖ Primär form:

- a) Hereditär, autosomalt dominant ärftlig, ca 1/3.
- b) Icke-hereditär s.k. idiopatisk.

## ❖ Sekundär form:

Fe-brist, uremi, graviditet, diabetes, radikulopati,  
B12-brist, folatbrist, RA, Porfyri, koffein, alkohol, nikotin,  
läkemedelsinducerad (SSRI, tricyklika, litium, DA-antagonister)



# Behandling

## ❖ Primär form:

- a) Icke-farmakologisk behandling
- b) Farmakologisk behandling

## ❖ Sekundär form:

- a) Behandling av bakomliggande sjukdom
- b) Ställningstagande till medicinutsättande (läkemedelsinducerad).
- c) Begränsa intag av koffein, alkohol och nikotin.
- d) Expektans (graviditet)



# Icke-farmakologisk behandling

- ❖ Skärpt sömnhygien
- ❖ Isometrisk muskelträning och/eller stretching före sänggåendet
- ❖ Massage, akupressur, avslappning
- ❖ TNS
- ❖ Kyla / Värme
- ❖ Mentalt distraherande aktivitet före sänggåendet
- ❖ Undvika hög fysisk aktivitet framförallt kvällstid.





# Farmakologisk behandling

## Dopaminerga medel

## Dosering

## Indikation

### Dopaminagonister

❖ Adartrel <sup>®</sup>	0.5–2 (4) mg t.n.	+
❖ Sifrol <sup>®</sup>	0.18-0.54 mg t.n.	+
❖ Neupro <sup>®</sup>	1-3 mg t.n.	+
❖ Cabaser <sup>®</sup>	0.5-2 mg t.n.	-
❖ Pravidel <sup>®</sup>	-	-

### L-dopa

❖ Madopark <sup>®</sup>	50-200 mg t.n.	-
❖ Madopark <sup>®</sup> Quick <sup>®</sup> Mite	50-200 mg t.n.	-
❖ Sinemet <sup>®</sup>	50-200 mg t.n.	-



# Farmakologisk behandling forts.

## Opioider

- ❖ Oxycodon (Targiniq<sup>®</sup>)
- ❖ Kodein (Kodein Recip<sup>®</sup>, Citodon<sup>®</sup>, Panocod<sup>®</sup>)

## Antiepileptika

- ❖ Gabapentin (Gabapentin<sup>®</sup>, Neurontin<sup>®</sup>)
- ❖ Pregabalin (Lyrica<sup>®</sup>)
- ❖ Karbamazepin<sup>®</sup> (Tegretol<sup>®</sup>, Hermolepsin<sup>®</sup>, Trimonil<sup>®</sup>)



# Farmakologisk behandling forts.

## Bensodiazepiner

- ❖ Clonazepam (Iktorivil<sup>®</sup>)

## Diverse

- ❖ Alfa-adrenostimulerare (Catapresan<sup>®</sup>)
- ❖ GABA-analoger (Lioresal<sup>®</sup>)



## Disordered sleep in Parkinsonism

„In this stage, the sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm. ... but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hanging, but even the floor and sashes of the the room.“

James Parkinson, An Essay on the Shaking Palsy, London 1817



# R(S)BD- Clinical Picture

- Violent or possible violent behaviour during REM sleep
- Movements related to dream contents, i.e. talking, laughing, screaming, hand movements
- Polysomnography: „REM sleep without atonia“
- The behaviour disrupts sleep continuity
- No epileptic activity, no seizures



# „Idiopathic“ RBD and RBD in PD

Schenck CH, Bundlie SR, Patterson AL, Mahowald MW **Rapid eye movement sleep behavior disorder. A treatable parasomnia affecting older adults.**

JAMA. 1987

Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, Lugaresi E, Cortelli P. **REM sleep behavior disorders in multiple system atrophy.**

Neurology. 1997

Comella et al: **Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease, Neurology. 1998**



# Pathophysiology of RBD

- ❖ RBD may represent a preclinical marker of a neurodegenerative process in synucleinopathies such as PD and MSA and may precede motor symptoms for years.

Olson EJ, Boeve BF, Silber MH: Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases, *Brain*. 2000;123:331-339.



## BASIC SCIENCE

# Increased Muscle Activity During Rapid Eye Movement Sleep Correlates with Decrease of Striatal Presynaptic Dopamine Transporters. IPT and IBZM SPECT Imaging in Subclinical and Clinically Manifest Idiopathic REM Sleep Behavior Disorder, Parkinson's Disease, and Controls

Ilonka Eisensehr<sup>1</sup> MD; Reiner Linke<sup>2</sup> MD; Klaus Tatsch<sup>2</sup> MD; Bitu Kharraz<sup>1</sup> Cand. Med.; Josef F Gildehaus<sup>2</sup> MD; Christian T Wetter<sup>3</sup> MD; Claudia Trenkwalder<sup>4</sup> MD; Johannes Schwarz<sup>5</sup> MD; Soheyl Noachtar<sup>1</sup> MD

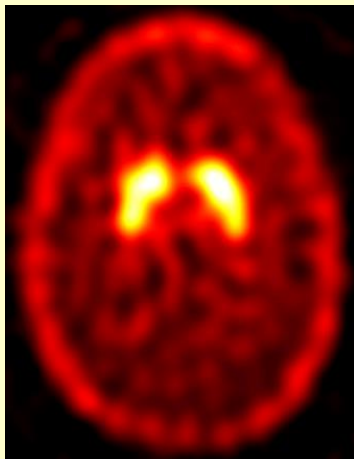
<sup>1</sup>Department of Neurology, University of Munich, Germany; <sup>2</sup>Department of Nuclear Medicine, University of Munich, Germany; <sup>3</sup>Max-Planck-Institute for Psychiatry, Munich, Germany; <sup>4</sup>Department of Neurophysiology, University of Goettingen, Germany, <sup>5</sup>Department of Neurology, University of Leipzig, Germany

Subclinical RBD correlates with the extent of presynaptic DAT binding in idiopathic RBD

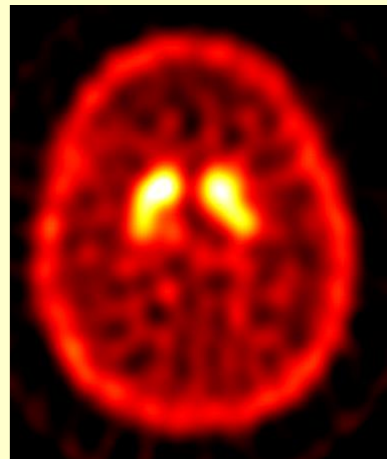


# Striatal IPT-Binding (presynaptic dopamine transporter)

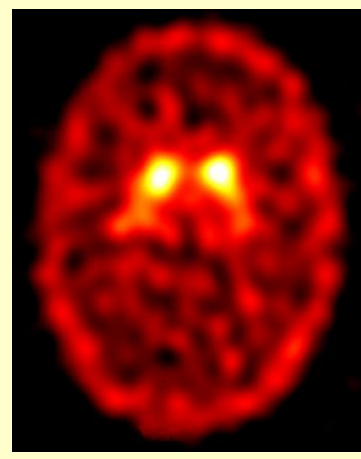
control      subclinical RBD      clinical RBD      PD



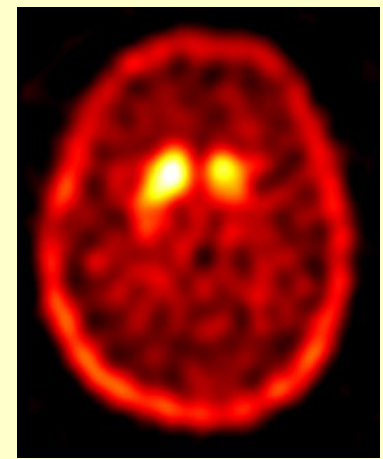
Ri: 4.47  
Le: 4.49



Ri: 3.62  
Le: 3.59



Ri: 2.88  
Le: 2.90



ipsi: 3.44  
contra: 2.46

*Eisensehr et al., Sleep 2003*  
*Eisensehr et al., Brain 2000*



## RBD as a preclinical marker

associated with:

❖ olfactory dysfunction

*Stiasny-Kolster et al, Brain 2005*

❖ reduced putaminal tracer uptake in DAT  
Scan

*Eisensehr et al, Brain 2000, Eisensehr et al, Sleep 2003*

❖ reduced MIBG-Spect

*Miyamoto et al, Sleep. 2008*



# Olfactory Dysfunction and RBD

- Olfactory tests in patients with idiopathic RBD (n=30)

clinical RBD: n = 19

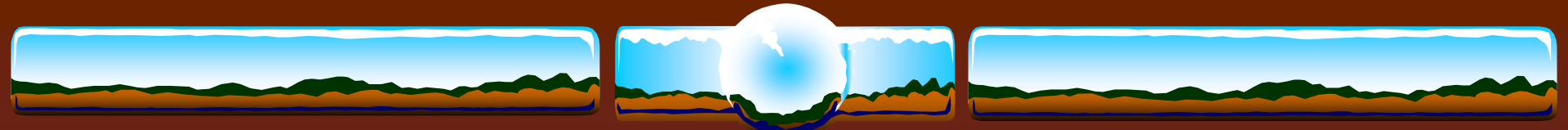
subclinical RBD: n = 11

- Olfactory threshold ↑ 97%
- Ability to identify smells ↓ 63%
- Ability to differentiate smells ↓ 63%

⇒ Patients with clinical and subclinical RBD show a dysfunction of olfactory abilities

*Stiasny-Kolster K, Doerr Y, Moller JC, Hoffken H, Behr TM, Oertel WH, Mayer G. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT.*

*Brain. 2005 Jan;128(Pt 1):126-37.*



# „Quantifying the risk of neurodegenerative disease in idiopathic RBD“

**Long-term follow-up of 113 patients with iRBD:**

Estimated risks for neurodegeneration:

- ❖ 5 years: 17.7%
- ❖ 10 years: 40.6%
- ❖ 12 years: 52.4%

Majority of patients developed PD and DLB



## RBD in PD: Prevalence?

### „REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease“

*Gagnon et al, Neurology 2002*

- ❖ 11/33 (30%) unselected consecutive PD patients showed RBD in PSG

### „REM sleep behavior disorder in sleep-disordered patients with versus without Parkinson's disease: is there a need for polysomnography“

*Eisensehr et al, J Neurol Sci 2001*

- ❖ 9/19 (47%) consecutive PD patients with subjective sleep complaints showed RBD on PSG



## Diagnostic gold standard: vPSG

- ❖ Poor sensitivity of specialized interviews for diagnosing RBD in PD patients by history

*Eisensehr et al, J Neurol Sci 2001*

- ❖ The diagnosis of RBD would have been missed in 50% of PD patients by history alone

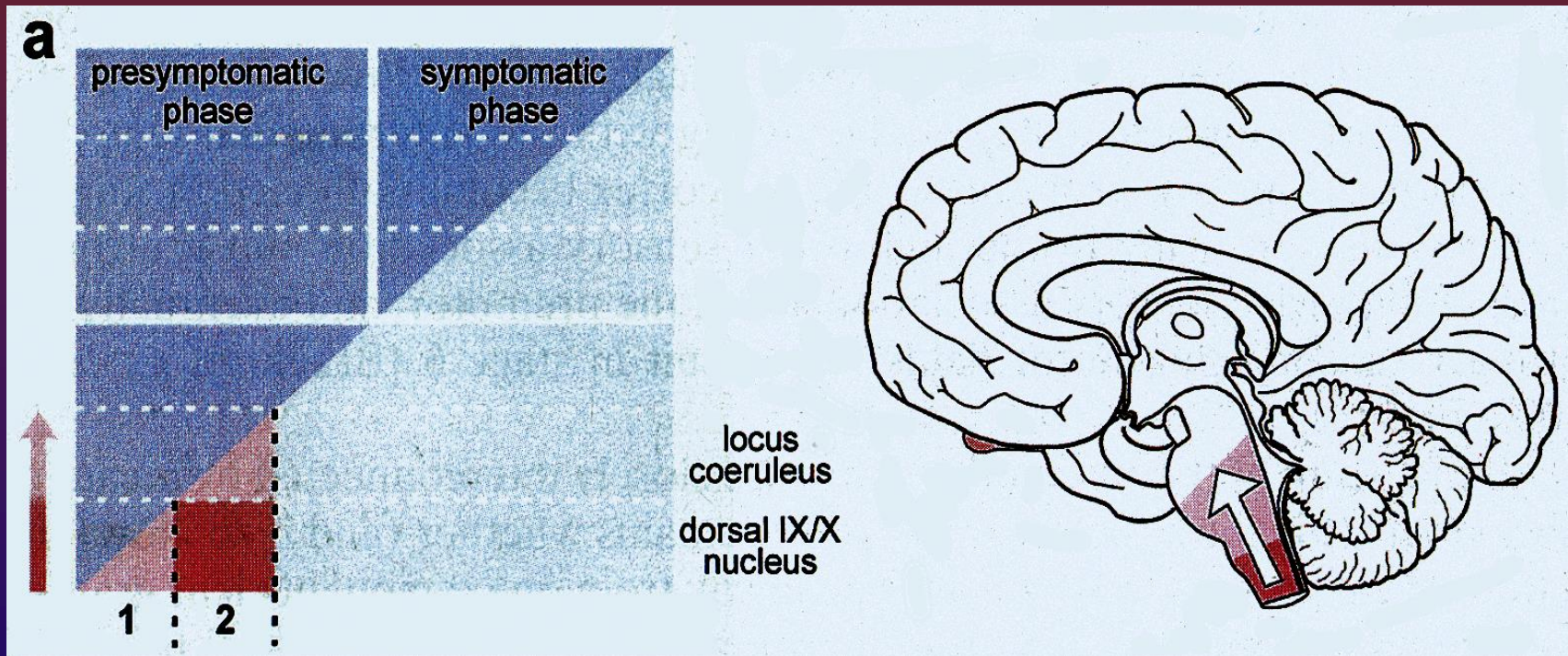
*Gagnon et al, Neurology 2002*



## RBD phenotype?

- ❖ **210/457 (46%) sleep disturbed PD patients showed RBD in vPSG**
- ❖ **Age was a significant predictor of RBD in this cohort**
- ❖ **Age-adjusted analysis showed longer disease duration, higher Hoehn&Yahr stages, more fluctuations and more falls in the PD+RBD group**
- ❖ **No preference of a motor subtype**
- ❖ **No higher prevalence of dementia**
- ❖ **No difference in perception of sleep quality (PDSS)**

# iRBD: Braak stages 1&2?







# Conclusion

Clinical RBD is an  
early **and** frequent  
sign in Parkinson syndromes  
(PD, LBD, MSA, PSP)



# Therapy of RBD

## **Clonazepam:**

**0.5mg – 1mg (2mg) at night**

*Schenck C, Mahowald M: A polysomnographic, neurologic, psychiatric and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89,5% of 57 treated patients, Clev Clin J Med. 1990;57:10-24.*

## **Melatonin:**

**2-4 mg Circadin 1-2 hours before bedtime**

## **Avoid SSRI for antidepressive treatment**

*Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia.  
Sleep. 2004 Mar 15;27(2):317-21*



# Sleep problems in PD

- ❖ Affects quality of life, hospitalization rates, treatment outcomes and relationships.
- ❖ Correlate with advanced age, duration and severity of the disease
- ❖ Under-reported