REM Sleep Behaviour Disorder (RBD)

to sleep, perchance to scream ….

a useful window into prodromal Parkinson's disease

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Overview

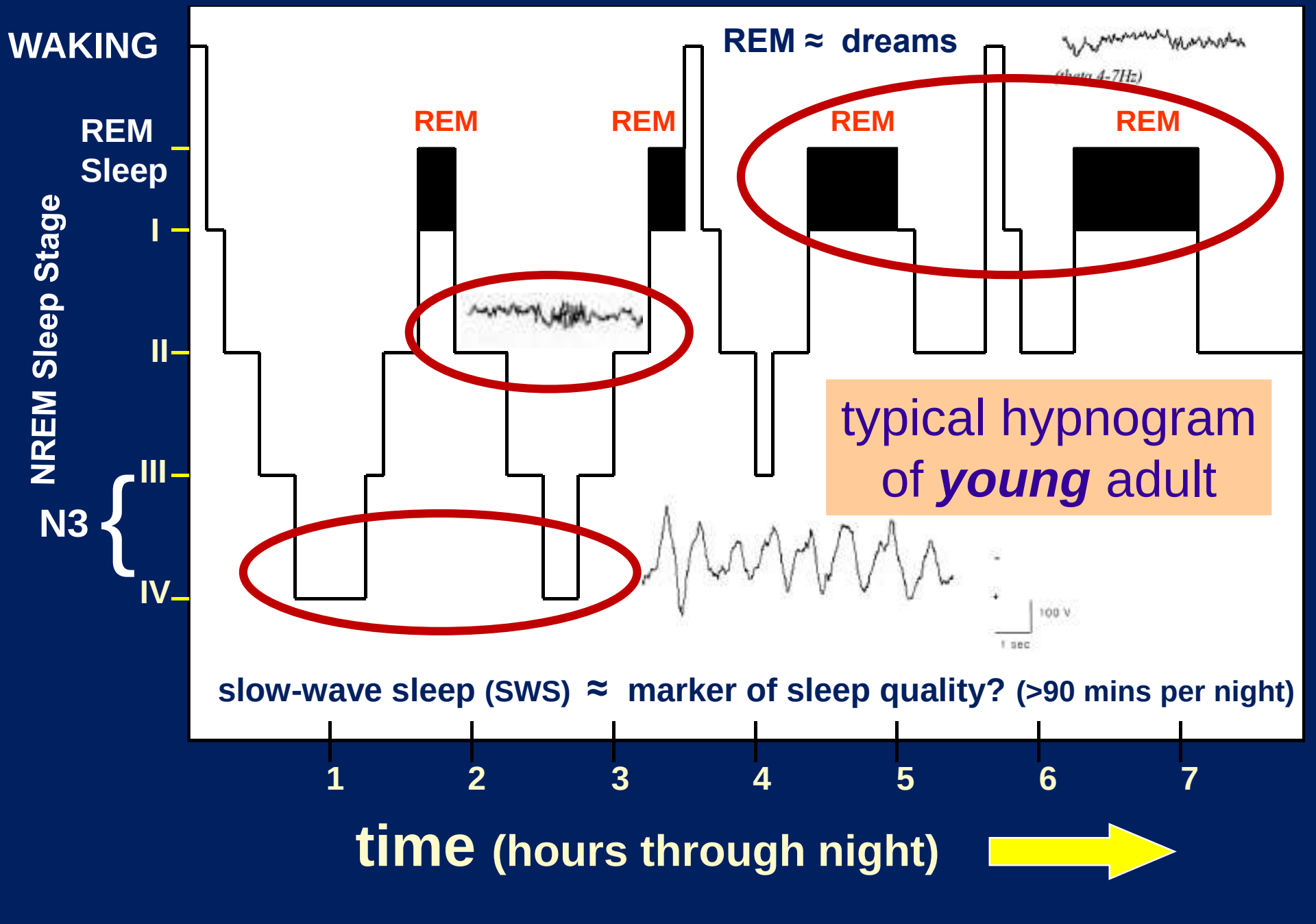
I. A (brief) biology of REM sleep

II. Idiopathic REM sleep behaviour disorder (i-RBD)

- clinical features and diagnosis
- neuroanatomical correlates
- secondary causes and mimics of RBD
- drug management
- the strong link to synucleinopathy

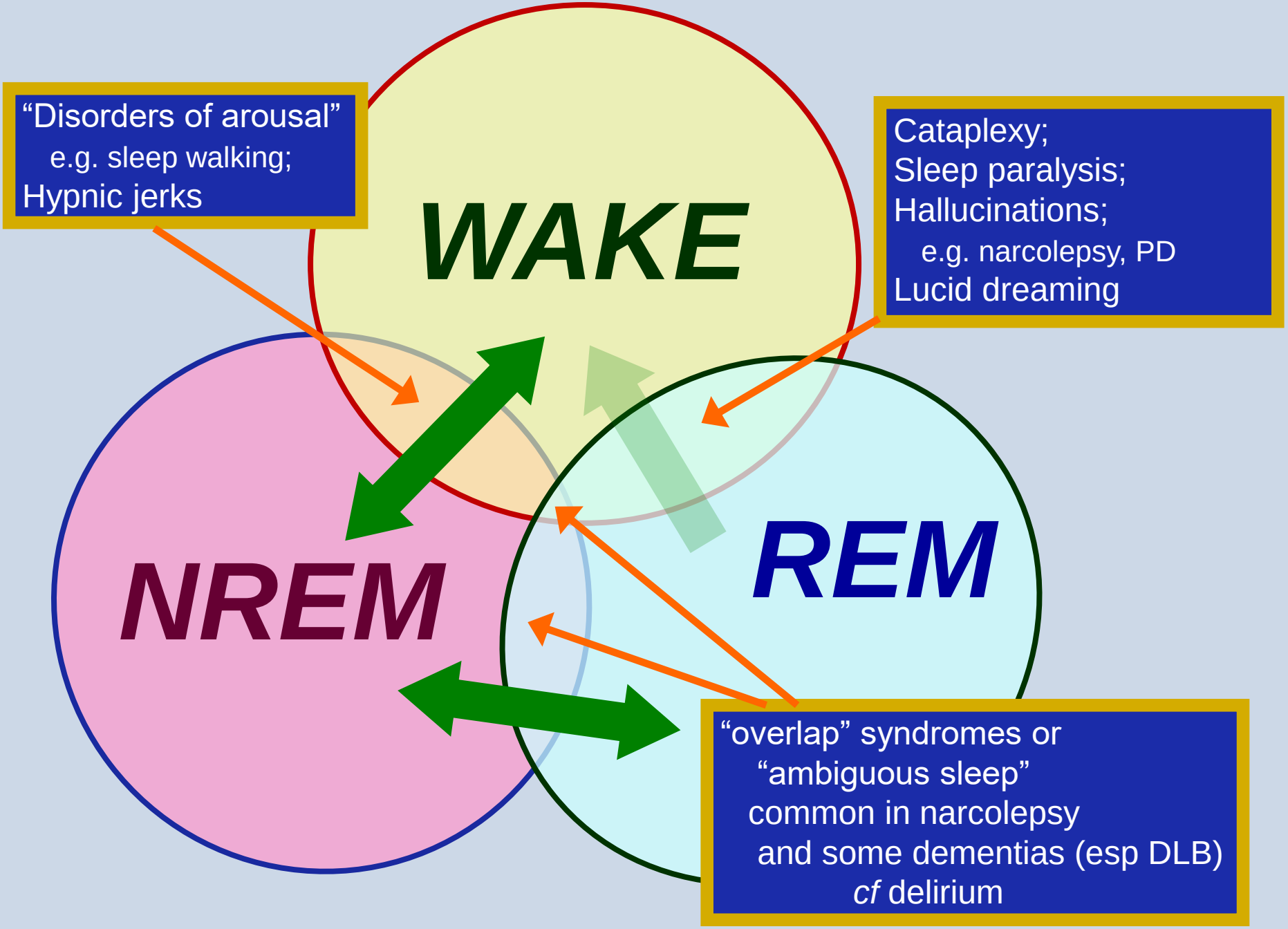
III. Neuroprotective trials in Parkinson's disease

- using RBD as a pre-clinical / prodromal marker


WAKING
REM Sleep
I
II
III
N3
IV
NREM Sleep Stage
REM ≈ dreams
REM
REM
REM
REM
typical hypnogram of *young* adult
slow-wave sleep (SWS) ≈ marker of sleep quality? (>90 mins per night)
1
2
3
4
5
6
7
time (hours through night)

	Wake	NREM sleep	REM sleep
Psychological features	Varying amounts of alertness and attentiveness	Unconscious, or bland thoughts	Vivid, story-like dreams
Physiological features	Sympathetic tone variable	Sympathetic tone low; roving eye movements in light NREM sleep	Sympathetic tone variable; bursts of fast saccadic eye movements
EEG pattern (5 sec)			
Developmental changes	Short wake bouts in infants and young children	Deep NREM sleep abundant in children, but gradually decreases across adulthood	Abundant in infants, steady levels across adulthood; NREM-REM cycle short in infants

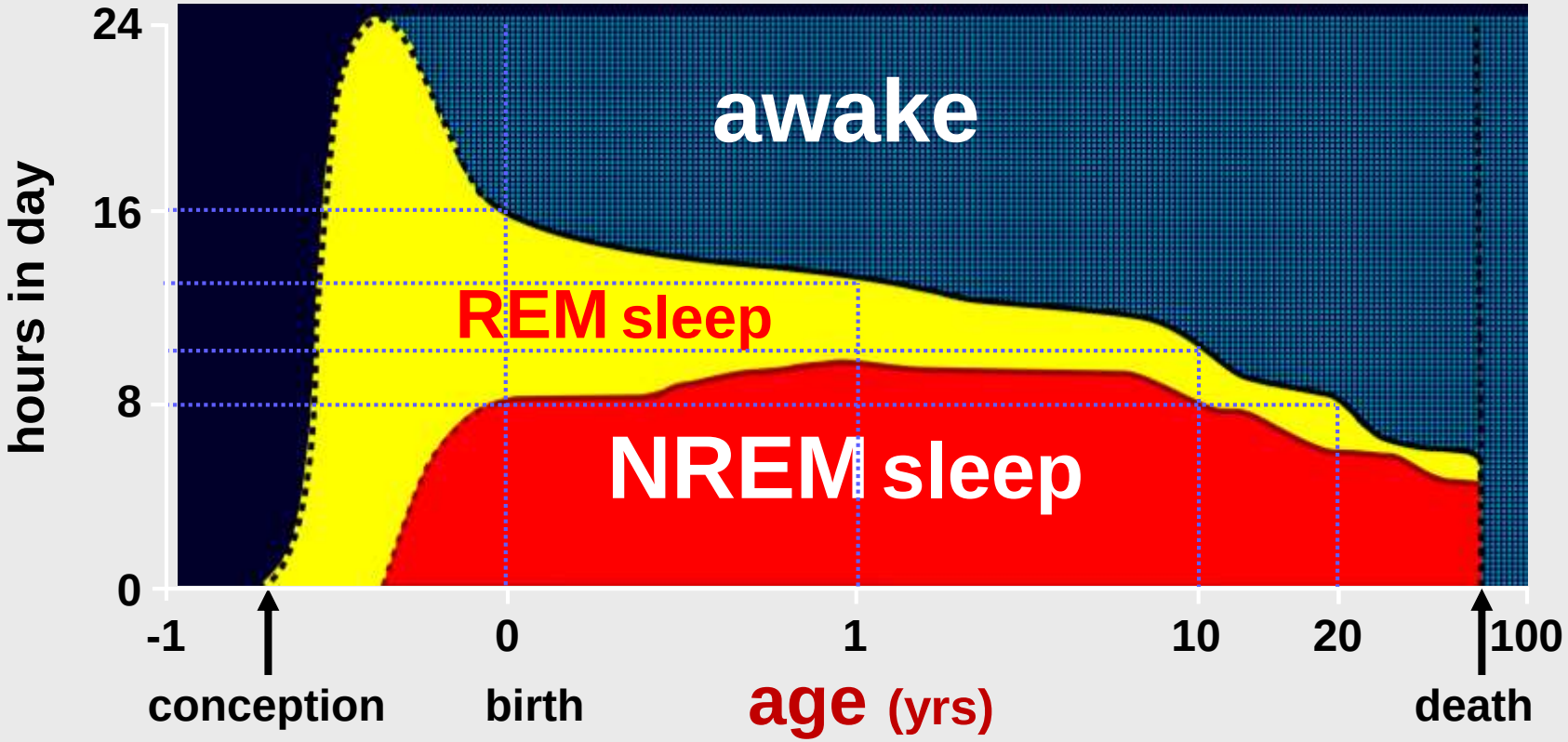
"a universal human experience occurring during sleep in which fictive events follow one another in an organized, storylike manner and into which are woven hallucinatory, primarily visual, images that are largely congruent with an ongoing confabulated plot"


"Disorders of arousal"
e.g. sleep walking;
Hypnic jerks
WAKE
Cataplexy;
Sleep paralysis;
Hallucinations;
e.g. narcolepsy, PD
Lucid dreaming
NREM
REM
"overlap" syndromes or
"ambiguous sleep"
common in narcolepsy
and some dementias (esp DLB)
cf delirium

REM sleep appears important (function?)

- the vast majority of animals exhibit a form of REM sleep
  - rats will survive only 4 weeks if REM sleep selectively inhibited
  - REM will "rebound" if suppressed (note: the "DT's")

- human neonates spend ~30% of 24 hr period in REM ("active") sleep



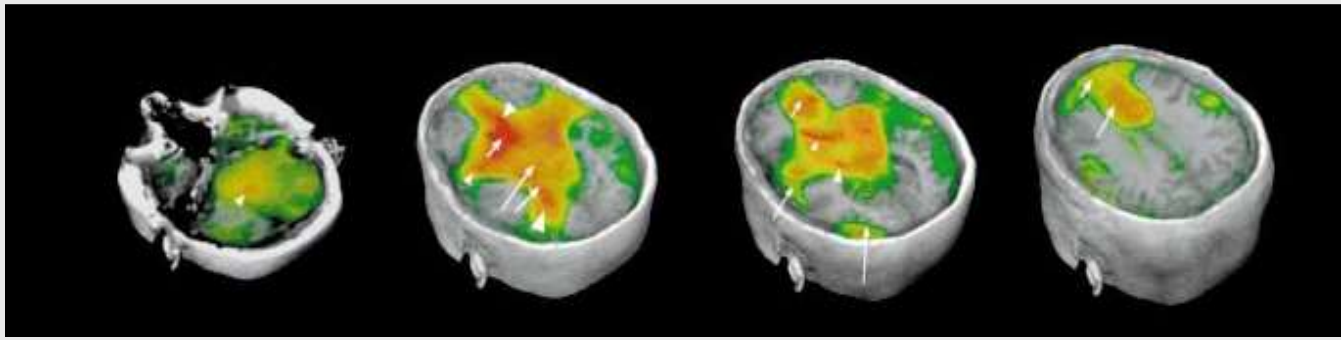
Features of REM sleep

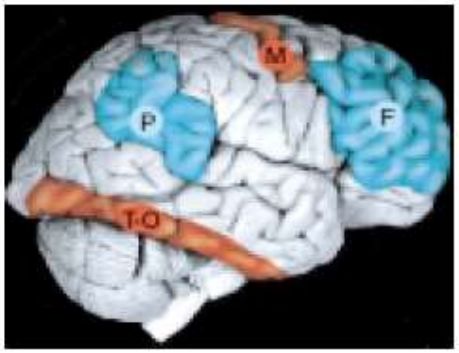
- **REM sleep should originate from state of non-REM sleep**
- **although unconscious, REM is a highly activated brain state**

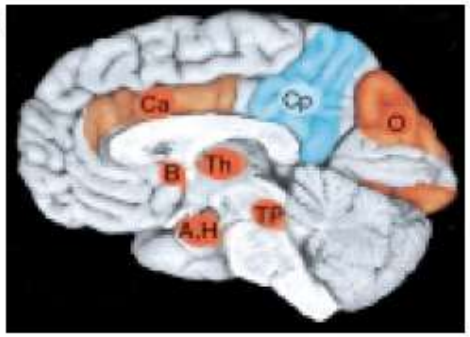
"paradoxical sleep" – selective cortical & limbic activation

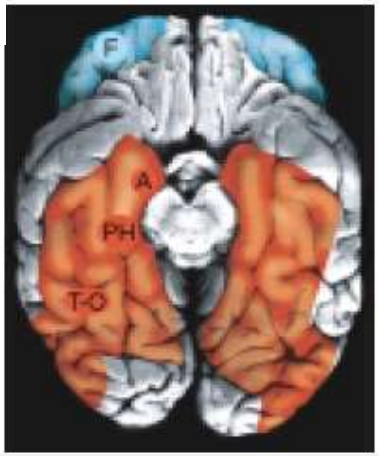
- PET data

(Braun *et al* 1997)









- summary of REM data

(Schwartz & Maquet 2002)

pons, midbrain, ventral striatum, amygdala, limbic cortex (ACC) all metabolically active

(note : dorso-lateral prefrontal cortex and hippocampus relatively underactive)

theta oscillations
hippocampus
basal forebrain

cortical activation
cortex
thalamus
basal forebrain

pontine reticular formation
GLUTAMINERGIC
LDT / PPN
CHOLINERGIC

PGO waves
occipital cortex ← lat genic nucleus

rapid eye movements
pontine reticular formation → colliculus
saccade generators

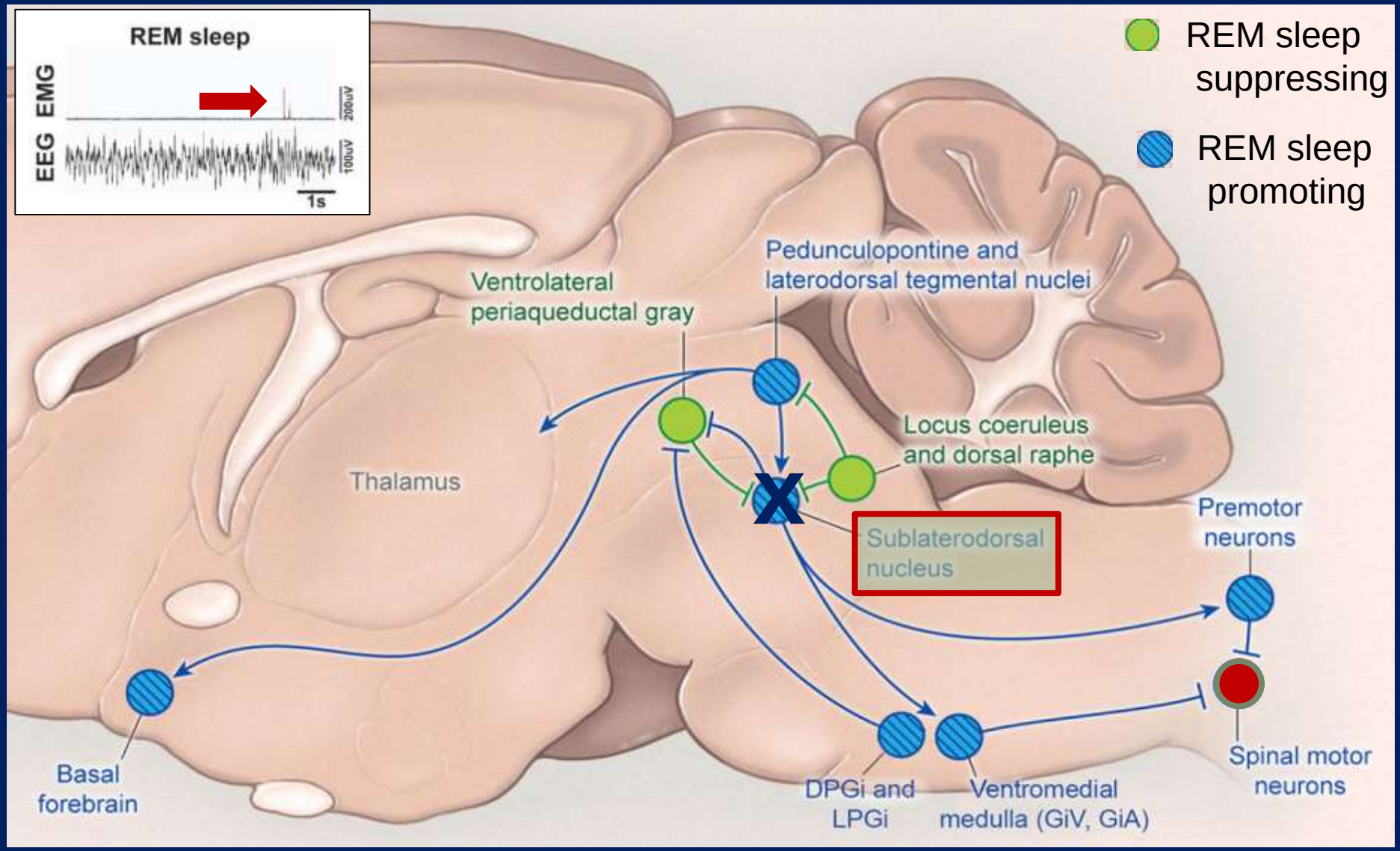
sub-coeruleus
medulla
GLYCINERGIC
motor neurons
muscle atonia

components of REM sleep

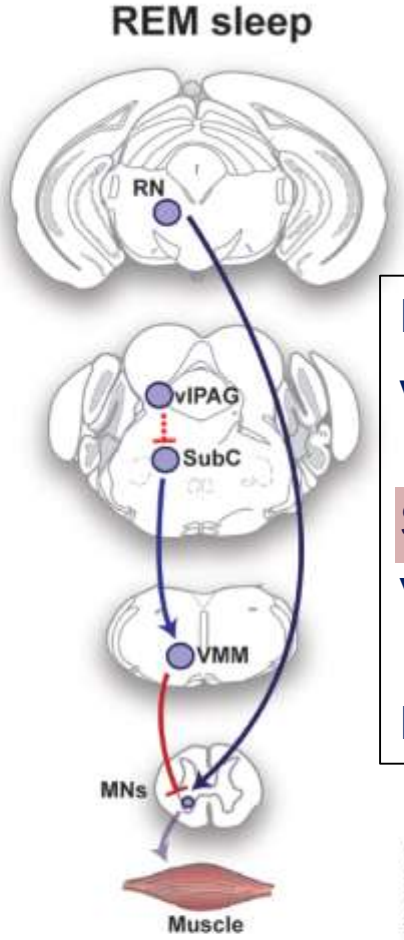
autonomic activation

- **heart rate / respiration**
- **pupillary constriction**
- **absent thermal regulation**
- **signs of sexual arousal**

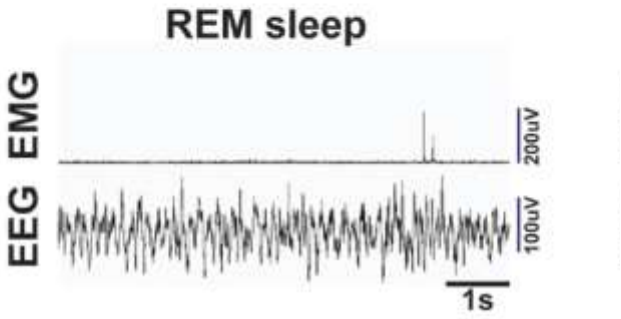
Neuro-circuitry of REM sleep (rat)

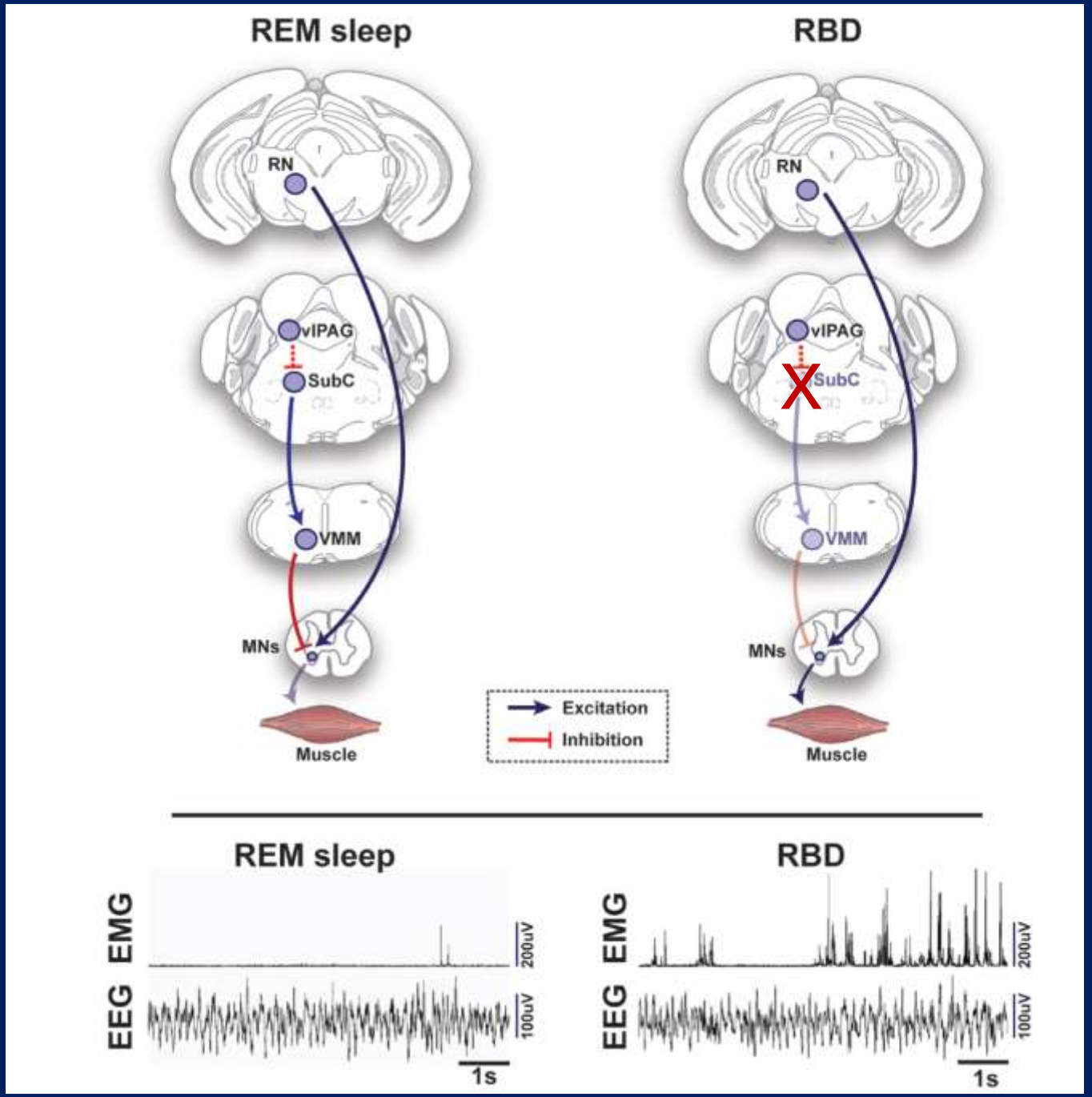


The neuroanatomy of REM sleep atonia



RN	red nucleus
vlPAG	ventrolateral periaqueductal gray
SubC	sub-coerulean complex
VMN	ventral medial medulla
MN	motor neurons

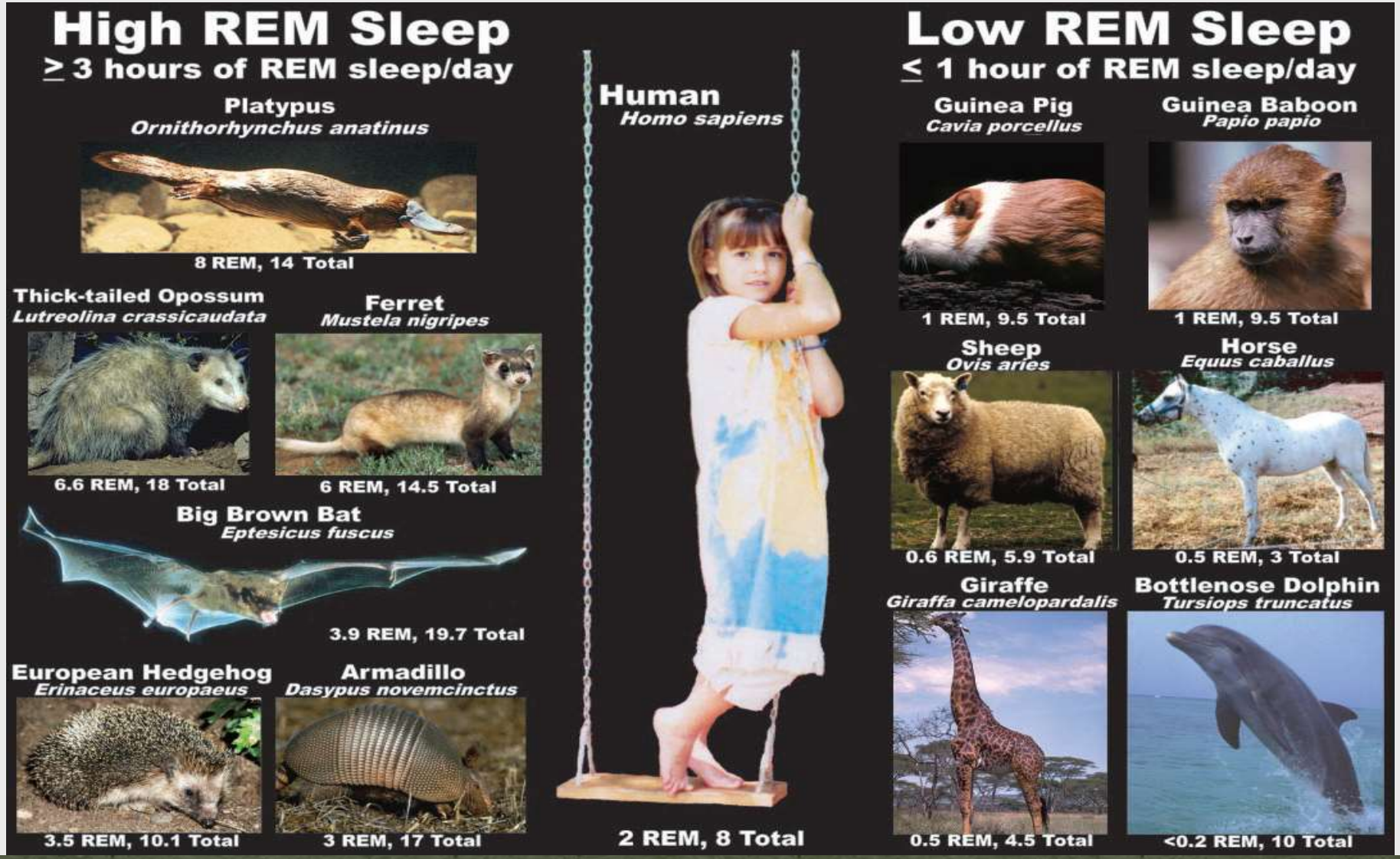



REM sleep
RBD
RN
vlPAG
SubC
VMM
MNs
Muscle
Excitation
Inhibition
REM sleep
RBD
EMG
EEG
200uV
100uV
1s

REM sleep across species

- **REM sleep conserved across majority of animal kingdom :**

  mammals, birds, reptiles (bearded dragon), invertebrates (cuttlefish), insects?



Is REM sleep dispensable?

- in early life, REM sleep particularly important?
  - note likely adverse effects for neuro-development / plasticity

    rat pups given daily clonidine / clomipramine:

    ↓↓cortical maturation, ↓hippocampal plasticity, behavioural effects

The importance of REM sleep for brain maturation

MAJID MIRMIRAN and EUS VAN SOMEREN

Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands

J. Sleep Res. (1993) 2, 188–192

- in adults, REM sleep suppression has little observable effect
- the vast majority of anti-depressants suppress REM (MAOI's)
  - shrapnel (pontine) lesion in 20 yr-old man (Lavie P. Neurology '84)

    no clear cognitive / behavioural sequelae seen 13 yrs after injury

    became a successful lawyer and crossword puzzle editor…..

- REM sleep simply a vestige from early development?
  - deep non-REM (slow wave) sleep more important in adults?

REM Sleep – a summary

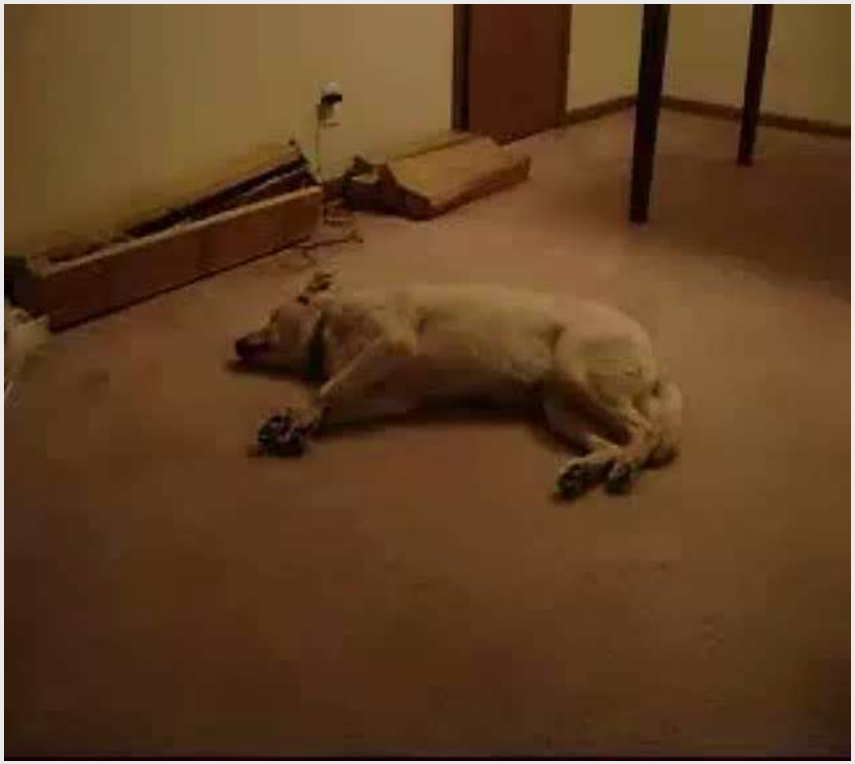
- REM sleep is a distinct and largely activated brain state
  - cortical activation similar to “wake” with cholinergic input
- REM sleep probably essential for vast majority of animals
  - particularly in early / neonatal period
- the neurochemistry/anatomy of REM sleep partially known
  - the regulation of NREM/REM may include a “flip-flop”mechanism
- full-blown narrative dreams mostly associated with REM
  - but sleep “mentation” very common in non-REM sleep
- there exist many theories of REM sleep (and dreaming)
  - (procedural/emotional) memory consolidation/targeted forgetting
  - emotional “regulation”
- is REM sleep a form of sophisticated “imaginative play” ?
  - safe “exercise” for the limbic lobe and autonomic system
  - prevents involution of neurons (if not used in daily waking life)

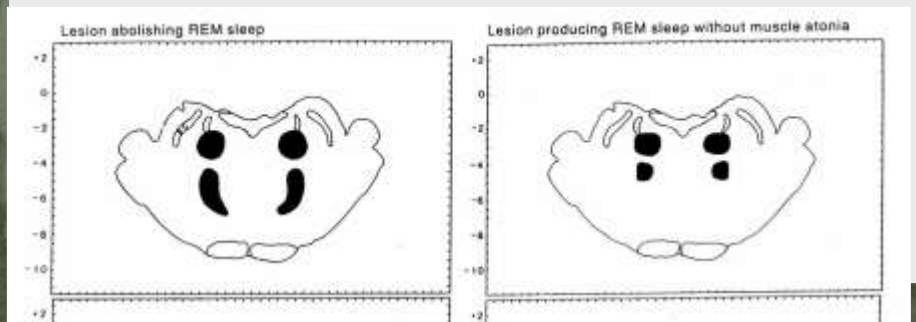
REM sleep in the clinic

REM sleep behaviour disorder (RBD)

Dream enactment in animals

- seen in cats (experimentally) and dogs (naturally…)





Recognising clinical features of RBD

- **In RBD:**
  - **subjects are generally elderly males (x6?)**
    simply less recognised in females?
    equal sex incidence if <50y
  - **no clear awareness of environment**
    not usually able to navigate or use objects;
    eyes generally closed
  - **subjects do not wander around**
    rare to leave the bed (but may fall out)
  - **attacks brief, explosive, recurrent**
    upper limbs typically involved
    vocalisation/swearing very common
  - **violence is unplanned / unintentional**
    victims are generally bystanders;
    usually defence rather than primary aggression
  - **fairly easy to arouse subjects from dream**
    when there is recall, normally unpleasant or violent themes, occasional sporting

The clinical spectrum of RBD

Defining REM Sleep Behaviour Disorder

Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep. 1986; 9(2):293–308. [PubMed: 3505730]

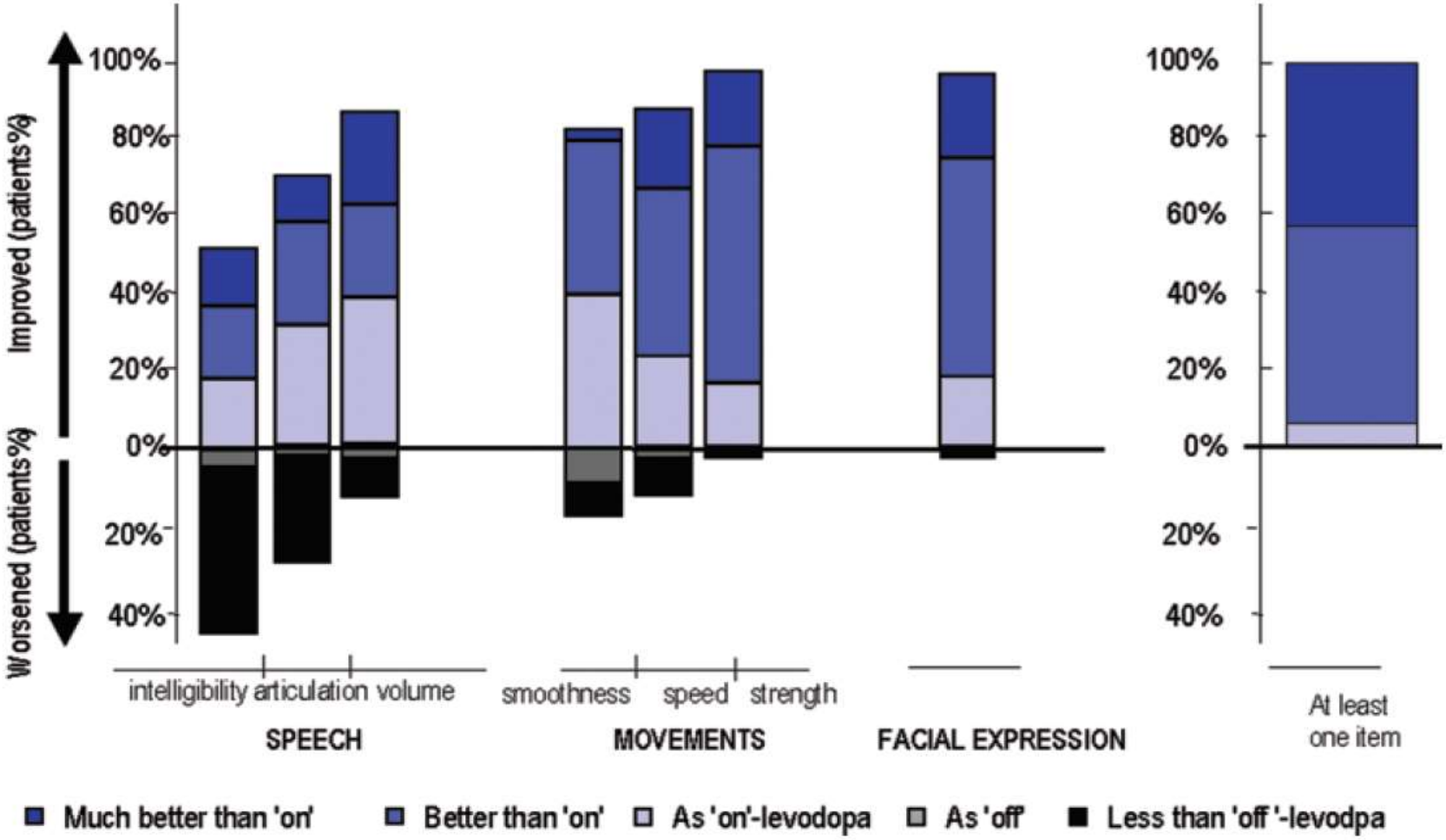
RBD is characterized by the intermittent loss of REM sleep electromyographic (EMG) atonia and by the appearance of elaborate motor activity (or vocalisation), associated with dream mentation, causing sleep disruption or injury (ICSD-3)

Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a Parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology. 1996; 46(2):388–93. [PubMed: 8614500]

- **latest accepted conversion rates to synucleinopathy are :**

5y → 33%; 10y → 74%; 14y → 91%

45% of those "converting" will develop iPD; 45% DLB; 5% MSA



in severe PD, RBD movements / speech all improved compared to wake

is the limbic system communicating directly with subcortical motor system?

basal ganglia bypassed ? (note *"kinesia paradoxica"* in PD)

de Cock *et al* Brain 2007

The clinical spectrum of RBD

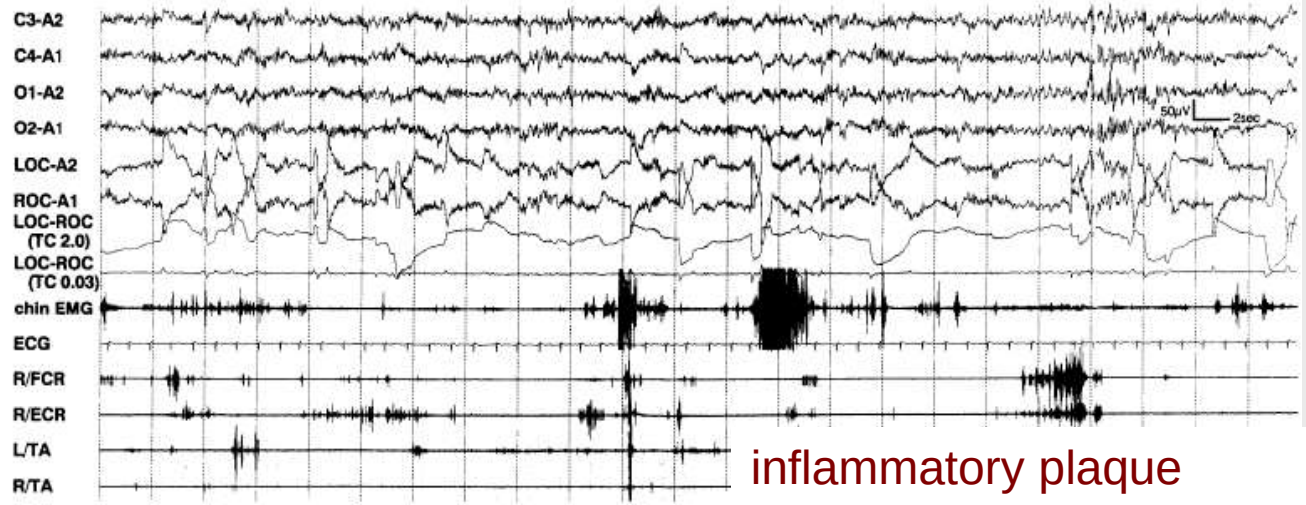
- RBD can be seen in younger populations (<40 yrs)
  - usually together with non-REM parasomnias ("overlap" syndrome)
- "RBD" relatively common in narcoleptic subjects (~30%)
  - a more benign phenomenon, pathology usually hypocretin ↓

- RBD associated with anti-depressants (and beta-blockers?)
  - venlafaxine and mirtazapine in particular?
  - also seen in benzodiazepine and alcohol withdrawal
- RBD a component of several auto-immune encephalitides

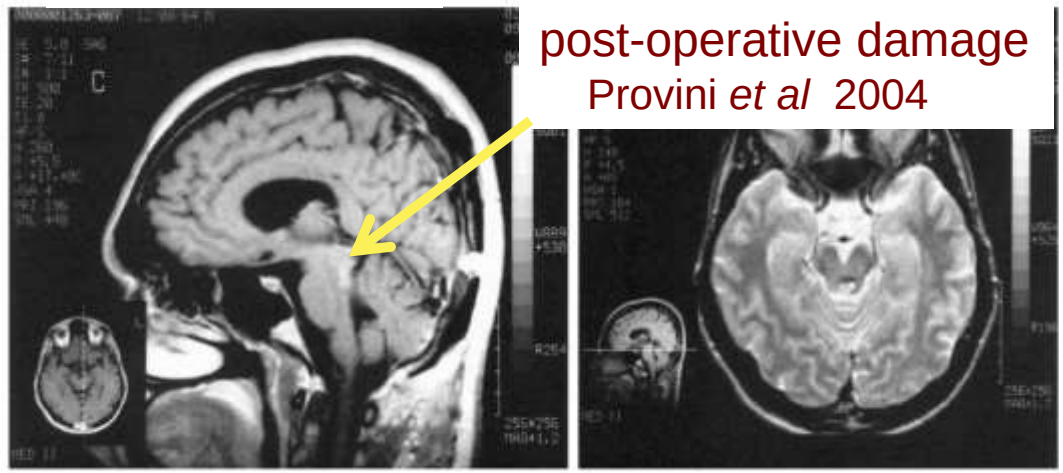
Discrete pontine lesions causing RBD

- numerous case reports of "secondary" RBD
  with variety of lesions usually in region of "locus subcoeruleus"

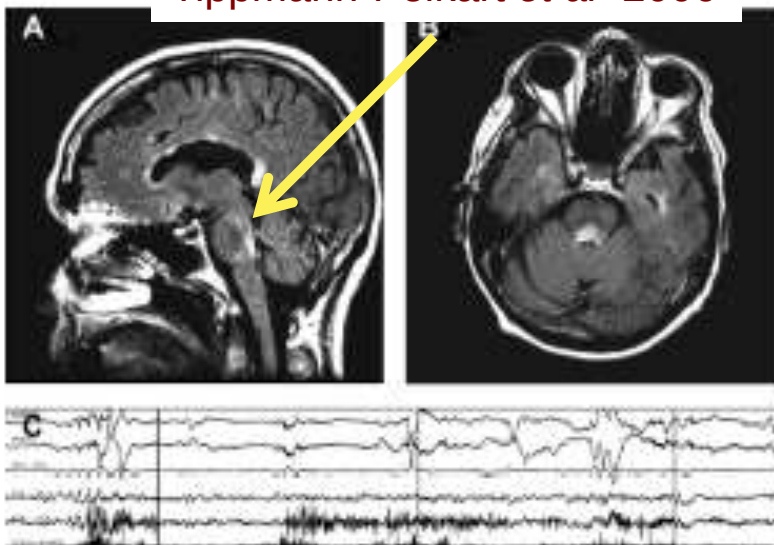
ischaemic lesion
Kimura *et al* 2000



inflammatory plaque
Tippmann-Peikart *et al* 2006



post-operative damage
Provini *et al* 2004



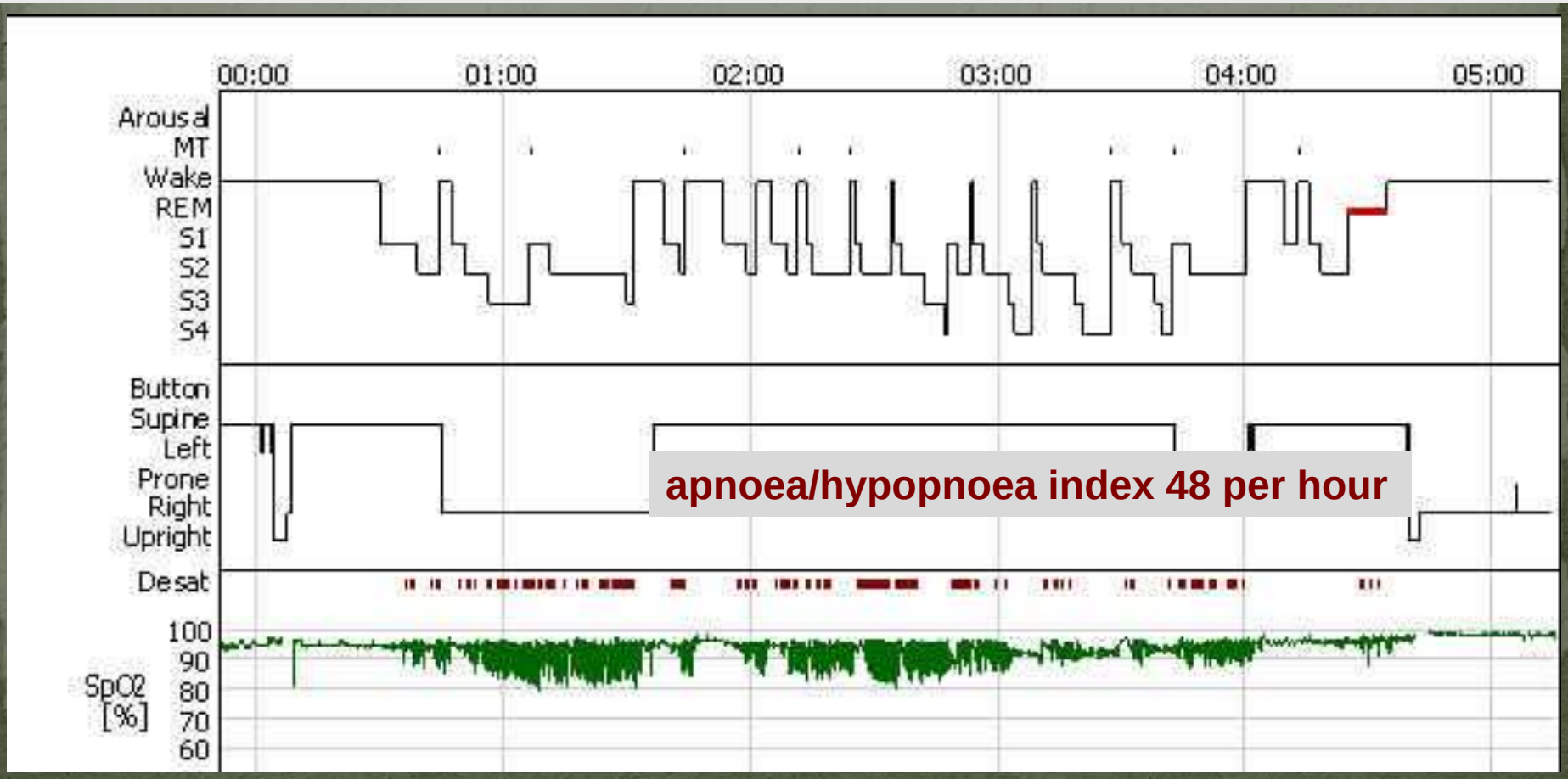
Mimics of RBD

sleep-related breathing disorder

- 63y ♂ PD (6yr history) with reported frequent nocturnal arousals occasional agitation / injury / confusion (little dream recall)

  mild EDS (ESS 12), known to snore, lives alone

  - no cognitive impairment, not overweight, receding chin noted



Management of RBD

- consider provoking or aggravating factors
  - majority of anti-depressants potentially worsen RBD
    particularly mirtazepine, venlafaxine?
  - beta-blockers? anti-histamines? caffeine?
- consider adjustments to sleeping environment
  - attend to furniture around bed
  - some prefer to use sleeping bags
  - limb restraints?

- drug therapy often warranted
  - long-term treatment generally needed

Drug management of RBD

no controlled drug trials

SPECIAL ARTICLES

JCSM
Journal of Clinical Sleep Medicine

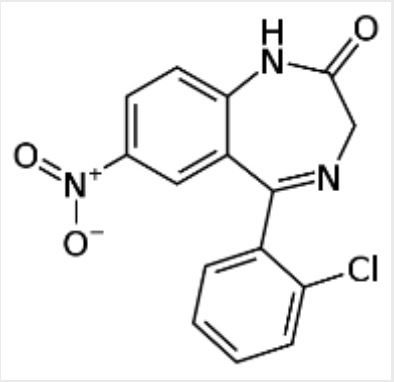
Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD)

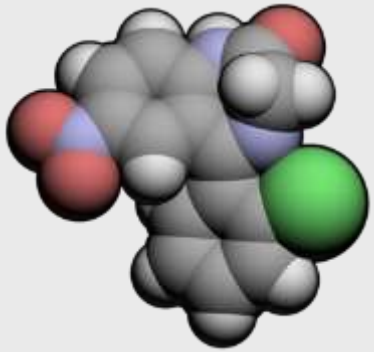
Standards of Practice Committee:

R. Nisha Aurora, M.D.[1]; Rochelle S. Zak, M.D.[1]; Rama K. Maganti, M.D.[2]; Sanford H. Auerbach, M.D.[3]; Kenneth R. Casey, M.D.[4]; Susmita Chowdhuri, M.D.[5]; Anoop Karippot, M.D.[6]; Kannan Ramar, M.D.[7]; David A. Kristo, M.D.[8]; Timothy I. Morgenthaler, M.D.[7]

Journal of Clinical Sleep Medicine, Vol.6, No. 1, 2010

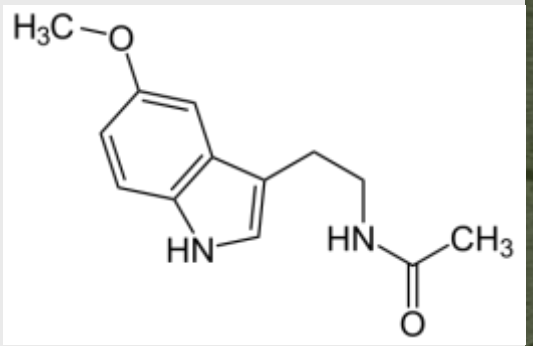
clonazepam

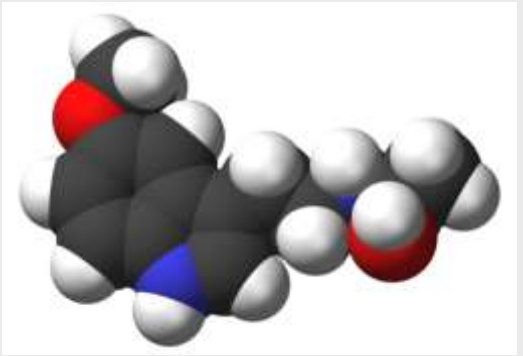




- 0.25 - 2 mg before bed
- effective in ~80%?
- care needed, especially if breathing-related disorder or dementia
- morning somnolence may limit use
- precise mechanism unknown
  - 5-HT action may be important
  - REM sleep not suppressed although eye movement density reduced
  - no direct effect on restoring REM atonia
  - are “locomotor” or dream generators inhibited?
- any PLM’s seen in association are usually effectively suppressed

melatonin





- 2-12 mg before bed
- long-acting preparations better?
- movement time reduced in REM sleep

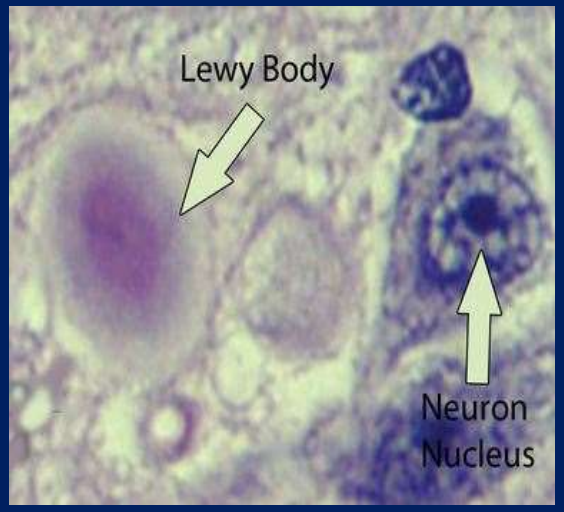
  normal atonia restored?

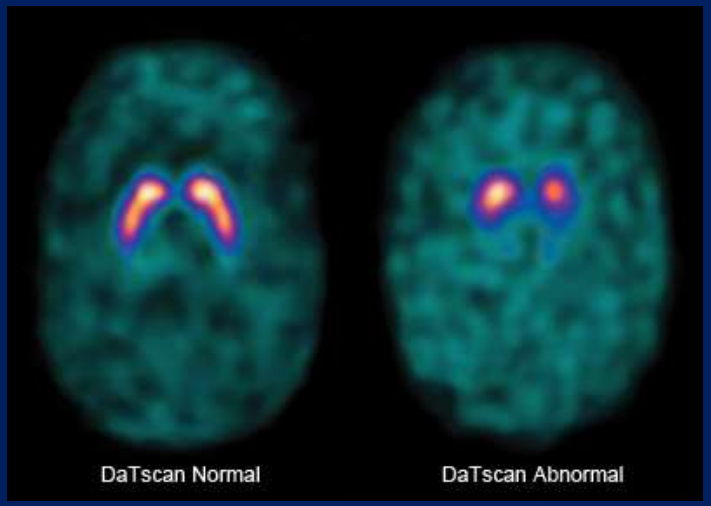
  Kunz and Bes Mov Disord 1999
- mechanism of action not known
- useful in combination with low dose clonazepam?

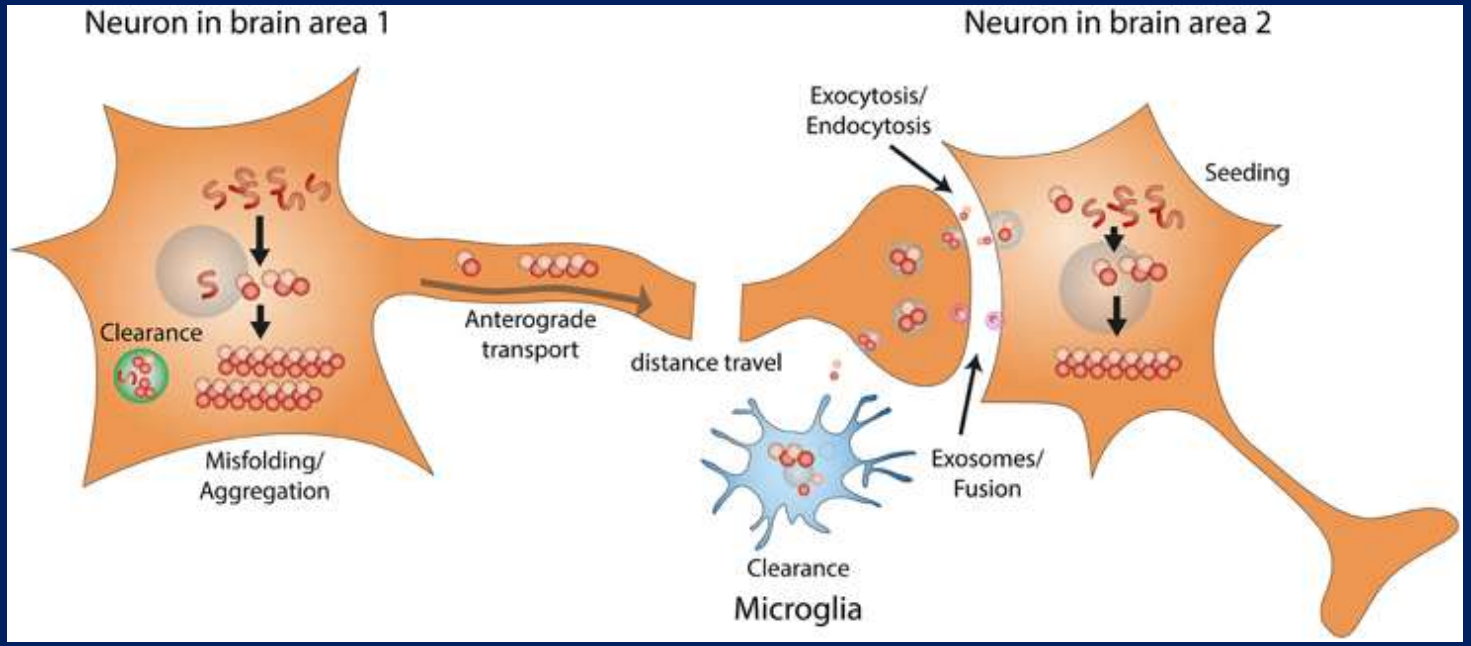
other drugs

- dopamine agonists
  - mixed / limited evidence for pramipexole
  - RBD unlikely to have a dopaminergic basis
- cholinesterase inhibitors
  - can improve or worsen RBD
- paroxetine
  - mixed evidence, of use in “cryptogenic” RBD?
    - 16 of 19 responded (Yamamoto *et al* Sleep Biol Rhythms 2006)
- other hypnotics including sodium oxybate

RBD and synucleinopathy





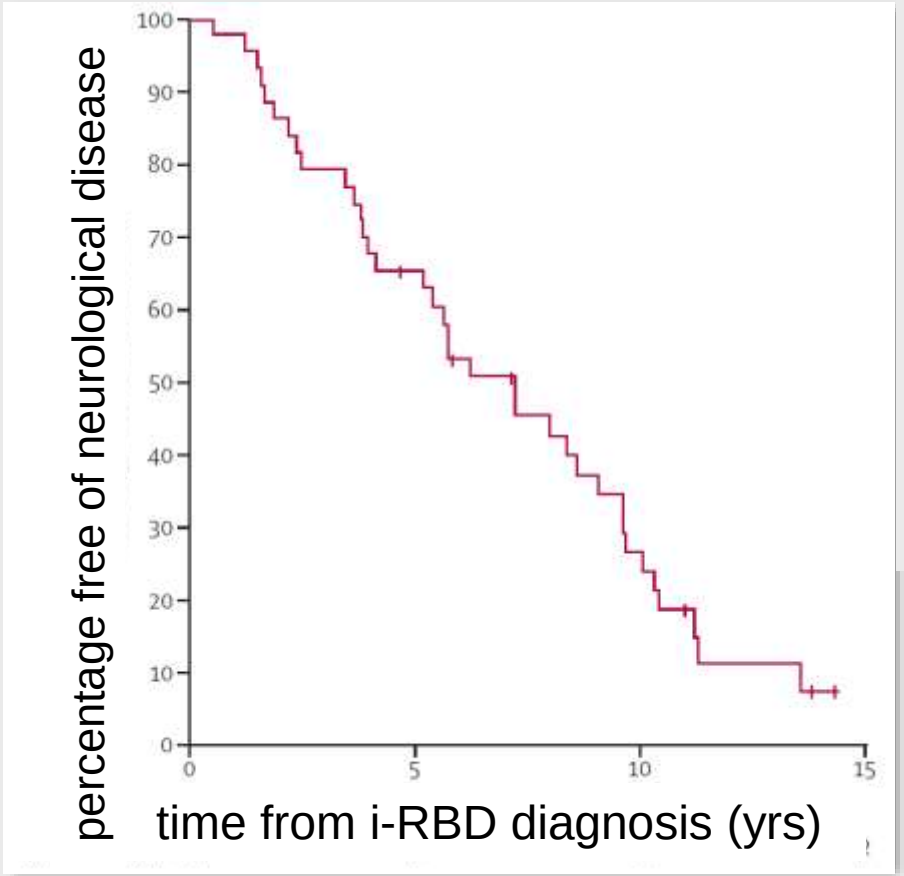


Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study

Alex Iranzo, Eduard Tolosa, Ellen Gelpi, José Luis Molinuevo, Francesc Valldeoriola, Mónica Serradell, Raquel Sanchez-Valle, Isabel Vilaseca, Francisco Lomeña, Dolores Vilas, Albert LLadó, Carles Gaig, Joan Santamaria

Lancet Neurol 2013; 12: 443–53

- **cohort study of 44 i-RBD patients recruited between 1991-2003**
  by 2012, 40 had developed clinical markers of neurological disease :



- 16 PD
- 14 DLB
- 1 MSA
- 9 MCI

of 4 remaining subjects:

all had >1 marker of possible Lewy body disease

- abnormal DAT scan
- hyposmia
- substantia nigra hyper-echogenicity

post-mortem on 3 confirmed wide-spread Lewy body pathology …

	Patient 1	Patient 2	Patient 3
General characteristics			
Sex	Male	Male	Male
Age at death (years)	82	74	81
RBD duration (years)	13	21	10
Parkinsonism duration (years)	2	3	7
Dementia duration (years)	2	No dementia	1
Antemortem diagnosis	DLB	PD	PD
α-synuclein stage,* neuronal loss and gliosis†			
Frontal cortex	2, +	1, acute infarct	1, +
Temporal cortex	3, + +	3, +	2, +
Parietal cortex	3, ++	1, acute infarct	1, +
Occipital cortex	1, +	0, +	0, 0
Anterior cingulate cortex	4, ++	2, +	3, +
Hippocampus CA2	2, +	2, ischaemia	3, 0
Entorhinal cortex	5, ++	2, +	2, +
Transentorhinal cortex	4, +++	2, +	2, +
Amygdala	4, ++	3, +	4, +
Olfactory bulb	4, not evaluable	2, not evaluable	3, not evaluable
Hypothalamus	3, +	2, +	3, +
Striatum	1, ++	1, acute infarct	2, +
Nucleus basalis of Meynert	3, ++	2, ++	3, +
Laterodorsal tegmental nucleus	1, ++	2, ++	2, ++
Pedunculopontine nucleus	2, ++	2, +	2, +
Substantia nigra pars compacta lateral tier	3, ++	3, ++++	3, ++++
Coeruleus/subcoeruleus complex	4/4, ++/++	3/3, ++/++	3/3, ++/++
Central raphe nucleus (pons)	3, ++	3, +	2, +
Dorsal motor nucleus vagal nerve	4, +++	3, +++	4, +++
Gigantocellular reticular nucleus	3, +	2, +	3, +

Is RBD an isolated clinical phenomenon?

Prodromal Parkinsonism and Neurodegenerative Risk Stratification in REM Sleep Behavior Disorder

Thomas R. Barber, MA, MBBS, MRCP[1,2]; Michael Lawton, MPhil[3]; Michal Rolinski , BA(Hons), MRCP[1,2,4]; Samuel Evetts, BSc (Hons), MSc[1,2]; Fahd Baig, BSc(Hons), MRCP[1,2]; Claudio Ruffmann, MD[1,2]; Aimie Gornall, BSc[1,5]; Johannes C. Klein, MD, PhD[1,2]; Christine Lo, BMedSci (Hons), MRCP[6,7]; Gary Dennis, BSc (Hons), MBChB, FRCP, MD[7]; Oliver Bandmann, MD, PhD[6,7]; Timothy Quinnell, MD, FRACP FRCP[8]; Zenobia Zaiwalla, FRCP, FRCPCH[9]; Yoav Ben-Shlomo, PhD[3]; Michele TM Hu, PhD, FRCP[1,2]

- large comparator study: 171 RBD; 296 control; 119 untreated PD
- RBD comparable to PD and worse than controls in numerous domains (detailed motor assessments, olfaction, cognition, dysautonomia)

  but *worse* than PD in measures of depression, anxiety, apathy
- anti-depressant use higher in RBD (compared to controls)
- i-RBD is truly prodromal PD & confers risk of more severe phenotype

RBD in established PD may predict a more aggressive clinical course

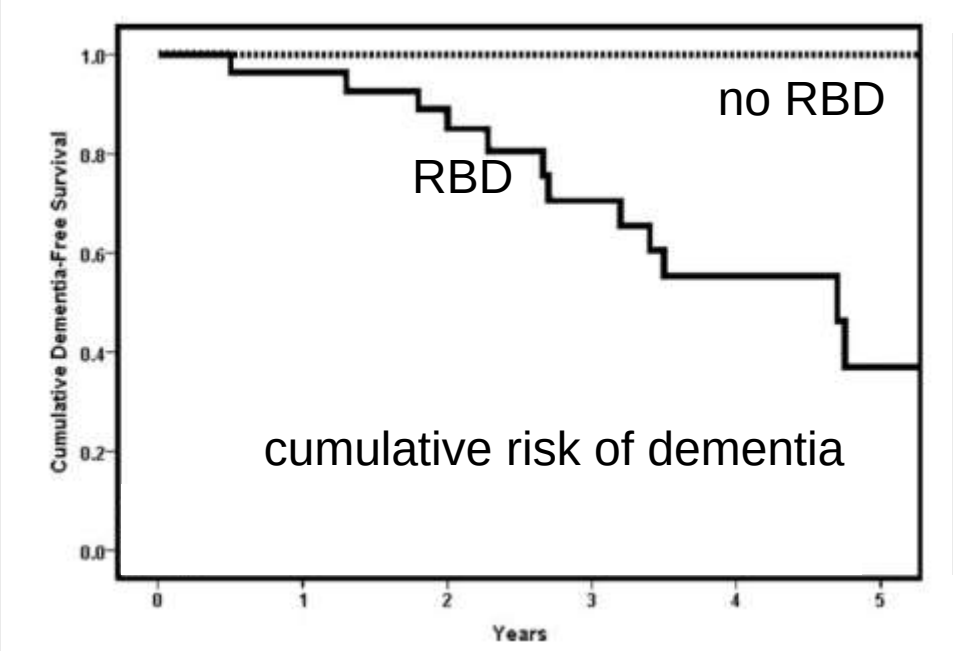
RESEARCH ARTICLE

Movement Disorders, Vol. 27, No. 6, 2012

Rapid Eye Movement Sleep Behavior Disorder and Risk of Dementia in Parkinson's Disease: A Prospective Study

Ronald B. Postuma, MD, MSc,[1,2*] Josie-Anne Bertrand, MPs,[2,3] Jacques Montplaisir, MD, PhD,[2,4] Catherine Desjardins, MPs,[2] Mélanie Vendette, MSc,[2,3] Silvia Rios Romenets, MD,[1] Michel Panisset, MD,[5] and Jean-François Gagnon, PhD[2,6†]

- **42 PD patients without dementia followed for 4y (27 RBD+; 15 RBD-)**



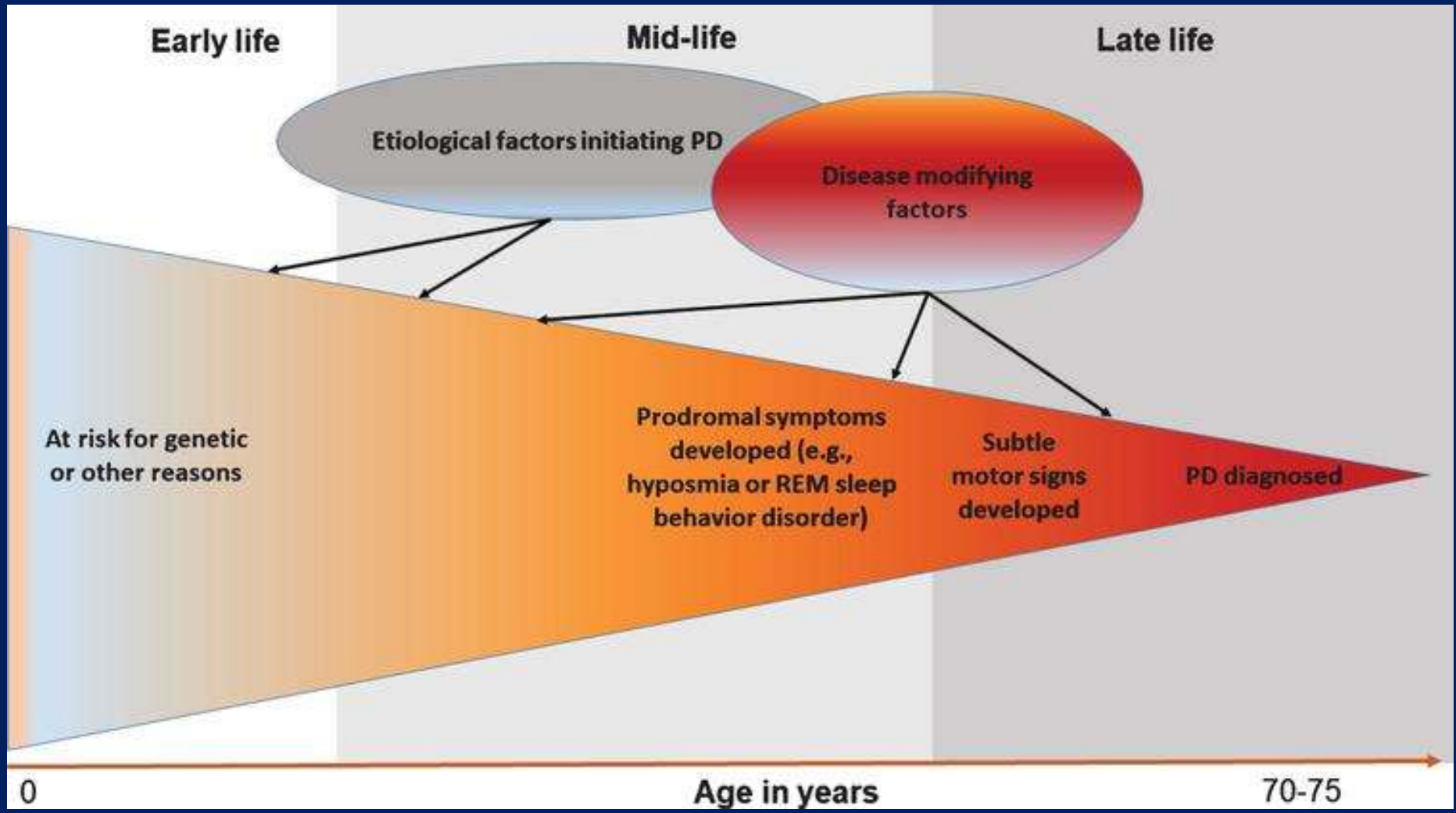
at baseline:

MCI in : 19 of 27 with RBD
4 of 15 without RBD

after 4y:

dementia in : 48% with RBD
0% without RBD

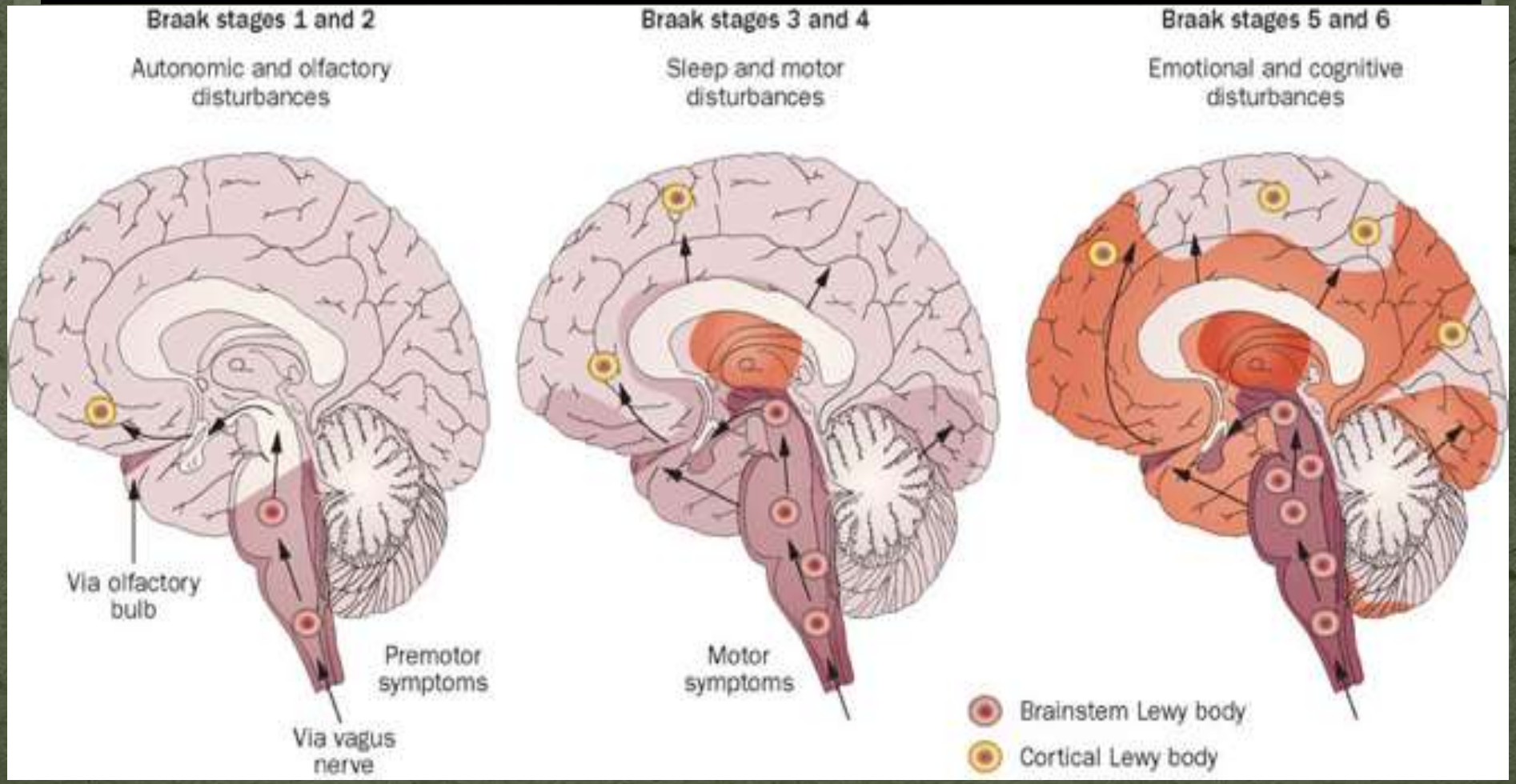
RBD and treatment trials for PD



Parkinson's Lewy body pathology may spread in a caudal to rostral pattern

(Braak hypothesis 2003)

does Lewy body pathology spread via a prion-like process?



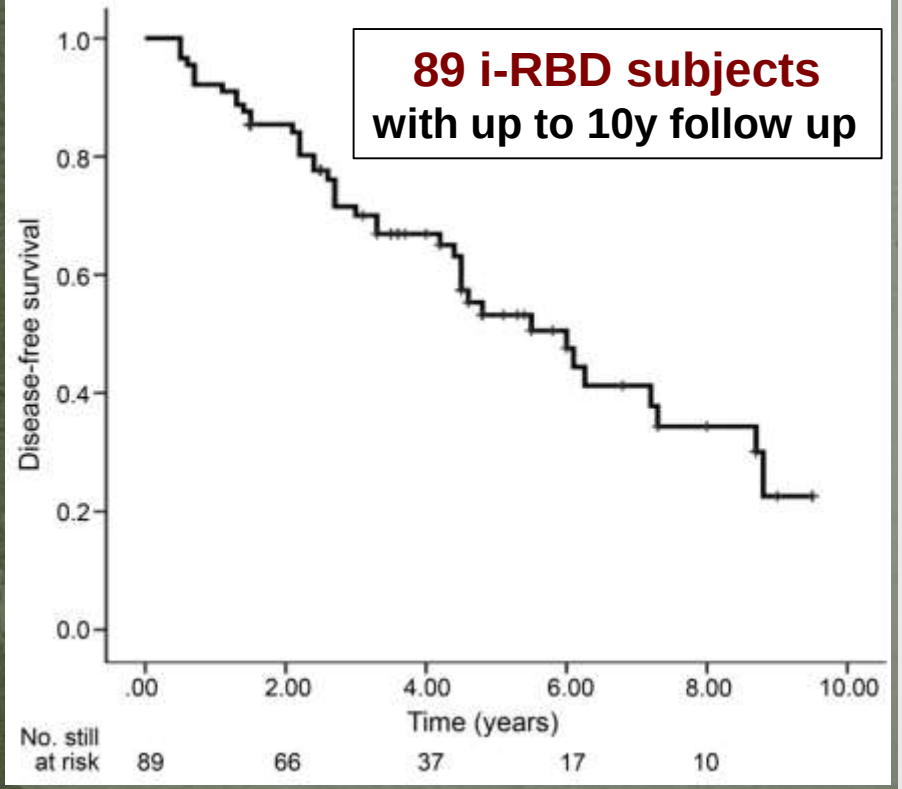
Predicting *early* "conversion"

Parkinson risk in idiopathic REM sleep behavior disorder

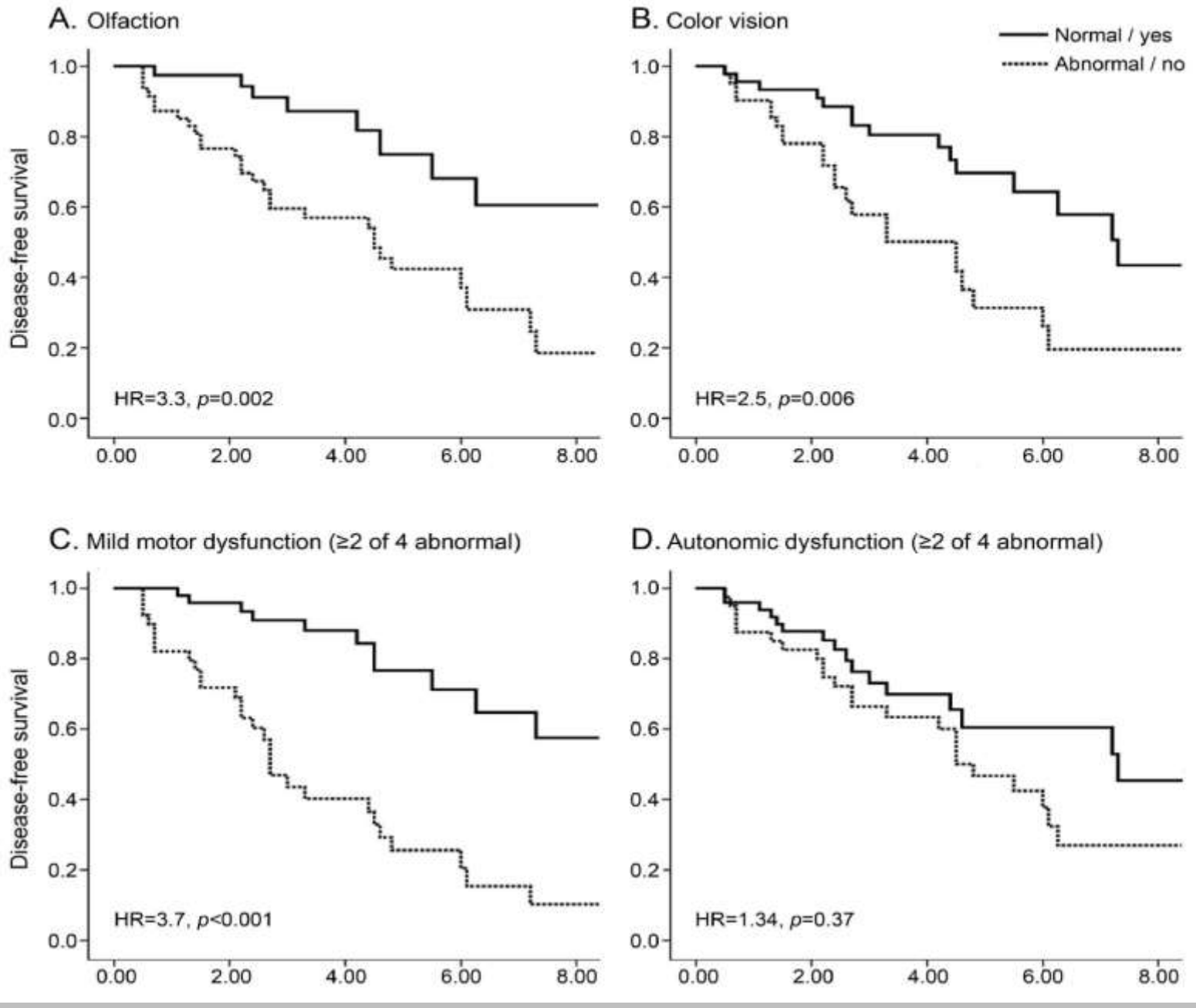
Preparing for neuroprotective trials

Ronald B. Postuma, MD
Jean-Francois Gagnon, PhD
Josie-Anne Bertrand, PhD
Daphné Génier Marchand, BSc
Jacques Y. Montplaisir, MD

Neurology® 2015;84:1104-1113



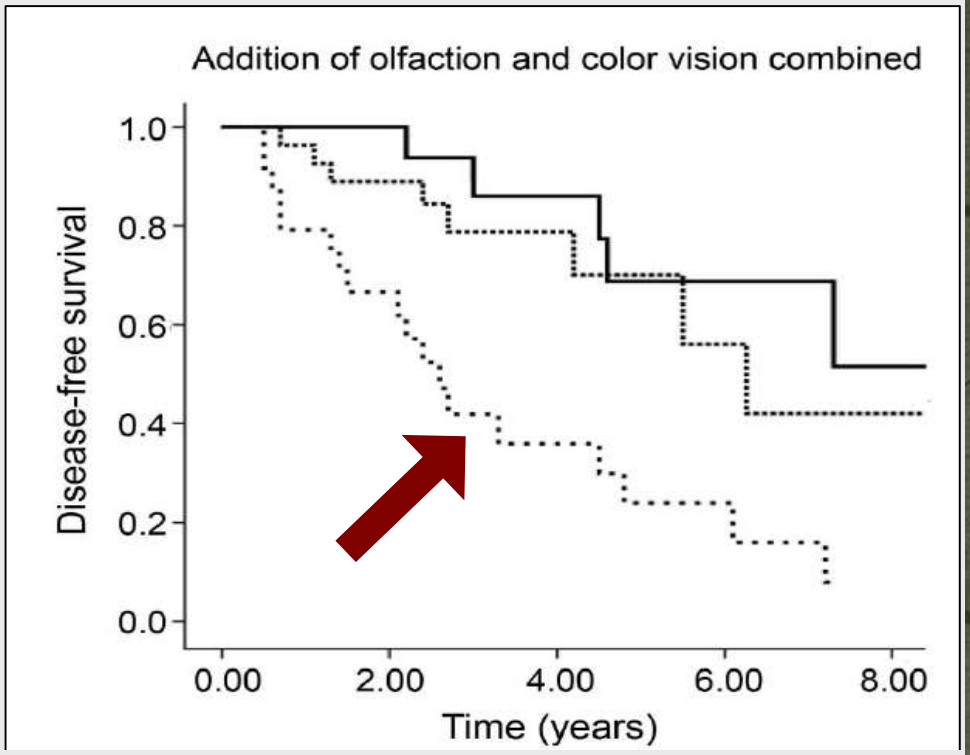
- **89 patients with >1y follow-up (2004-12)**
  - **80% developed neurodegenerative disease**
  - **~50% fulfilled DLB criteria**
  - **~50% PD (25% with MCI)**
- **all patients also fully assessed for:**
  - **- olfaction**
  - **- antidepressant use**
  - **- use of clonazepam/melatonin**
  - **- depression**
  - **- cognitive impairment**
  - **- colour vision**
  - **- autonomic symptoms**
  - **- pegboard and tap test performance**


A. Olfaction
B. Color vision
Normal / yes
Abnormal / no
Disease-free survival
1.0
0.8
0.6
0.4
0.2
0.0
HR=3.3, p=0.002
HR=2.5, p=0.006
0.00
2.00
4.00
6.00
8.00
C. Mild motor dysfunction (≥2 of 4 abnormal)
D. Autonomic dysfunction (≥2 of 4 abnormal)
HR=3.7, p<0.001
HR=1.34, p=0.37

- **study confirms high "conversion" rates of i-RBD to synucleinopathy**

- **other likely prodromal factors increase risk further :**

  - advanced age
  - reduced olfaction
  - altered motor function
  - poor colour vision
  - mild cognitive impairment



- **by stratifying RBD cohorts :**

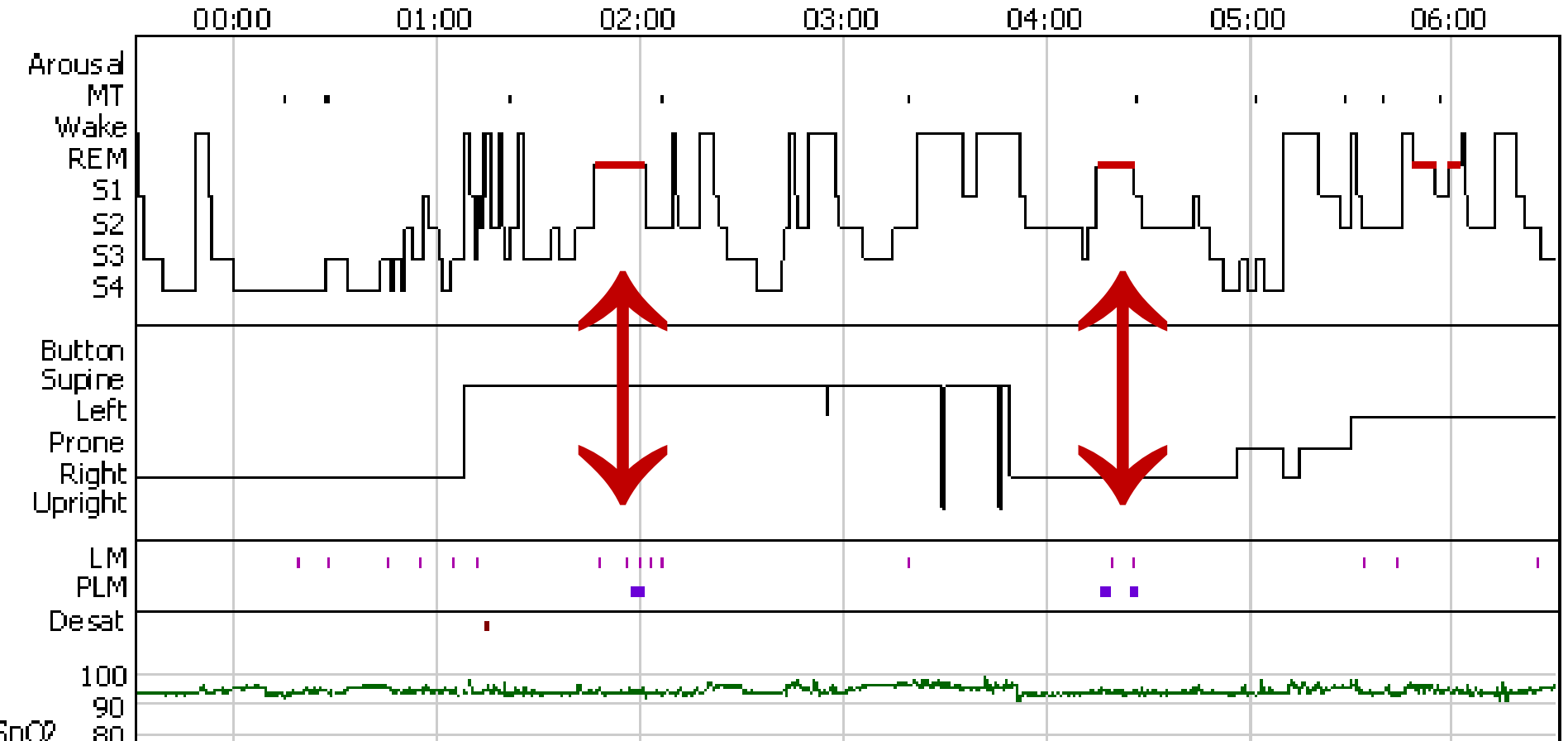
  sub-populations can be identified with *65%* risk of conversion within *3 yrs*

_if_ a moderately effective neuroprotective agent were available:

RCT trial of *~80 patients* in high risk group would provide sufficient power

Other potential features increasing future risk of neurodegeneration in RBD subjects?

- 59 yr-old male with 1 year history strongly suggestive of RBD
  - also reported significant sleep fragmentation / daytime sleepiness (ESS 14)
  - no other clinical features of note but developed severe DLB within 2yrs



Will imaging help refine the future risk of clinical progression in RBD subjects?

Research Article Ann Neurol 2017;82:419–428

Annals of NEUROLOGY An Official Journal of the American Neurological Association and the Child Neurology Society

Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder

Alex Iranzo MD

- 87 i-RBD subjects compared to 20 controls on DAT-SPECT scan
  - considered abnormal if >2 SD's less than control mean levels
  - follow-up mean 5.7y later
  - 25 converted (11 PD, 13 DLB, 1 MSA), mean 3.2y

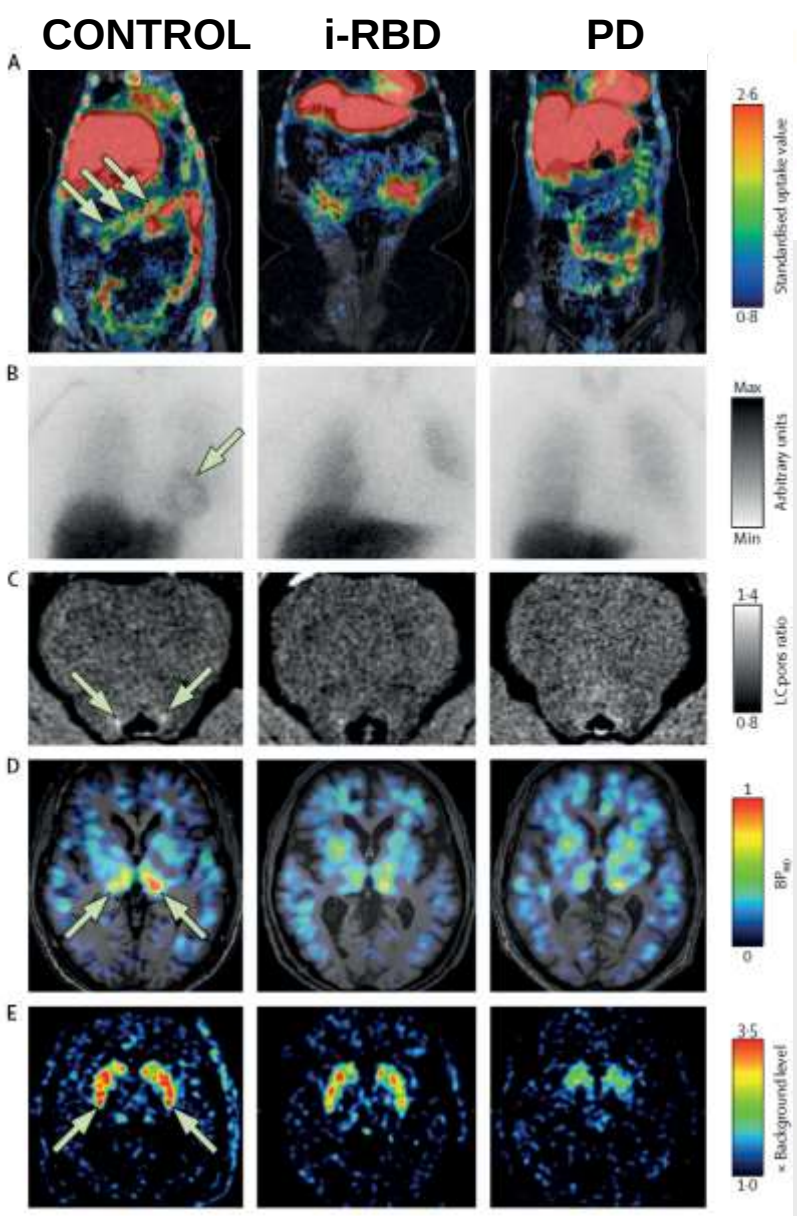
- baseline DAT deficit in 51 (60%) of i-RBD

  if DAT abnormal : risk 20% at 3y, 33% at 5y

  if DAT normal : risk 6%, at 3y, 18% at 5y

- if putaminal signal <25%, DAT has 75% sensitivity at 5y
  - 80% negative predictive value
  - likelihood ratio 1.54

Will imaging help refine the future risk of clinical progression in RBD subjects?



In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study

Karoline Knudsen*, Tatyana D Fedorova*, Allan K Hansen, Michael Sommerauer, Marit Otto, Kristina B Svendsen, Adjmal Nahimi, Morten G Stokholm, Nicola Pavese, Christoph P Beier, David J Brooks, Per Borghammer

Lancet Neurol 2018; 17: 618–28

- 22 Danish i-RBD (PD and controls):
  - gut para-sympathetics (PET/CT)
  - cardiac sympathetics (MIBG)
  - LC pigmented neurons (7T MRI)
  - thalamic NA termimals (PET)
  - dopamine in BG (F-DOPA-PET)
- i-RBD group same changes as PD *except* F-DOPA (71% RBD were normal)
- autonomic imaging changes profound in i-RBD subjects without signs of PD
- supports very early pathology in peripheral autonomic system with caudo-rostral spread to brainstem
- note recent skin / salivary gland data

Summary

- RBD pathology involves the sub-cerulean complex (loss of REM atonia)
  - abnormal (aggressive) dream content in (male) RBD unexplained
  - activation of a direct limbic-motor pathway produces movement?
- "Isolated" RBD predicts the development of neurodegenerative disease
  - within 15 years at least 90% of subjects "convert" clinically
  - a more "severe" PD phenotype (autonomic *Sx*, tremor ↓, cognition ↓)
- RBD associated with other prodromal PD markers confers extra risk
  - may allow patient selection for practical neuroprotective trials
  - but not yet clear which factors predict ***early*** conversion (<3yrs)
  - imaging / biomarkers (salivary gland synuclein?) likely to be useful
  - ethical issues remain as does need for a therapeutic agent (!)
- Some subjects have longstanding RBD (>10yrs) with no progression
  - even with early presence of prodromal markers
- Note: not all PD / DLB patients will display RBD (~40%)
  - will any results of neuroprotective trials apply to all PD patients?

Madness is a long dream;
A dream is a short madness