

REM Sleep Behavior Disorder and Neurodegenerative Disease

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Disclosure

- Financial-I have no financial conflicts of interest to declare
- Off Label Use-I will not discuss off-label therapies.

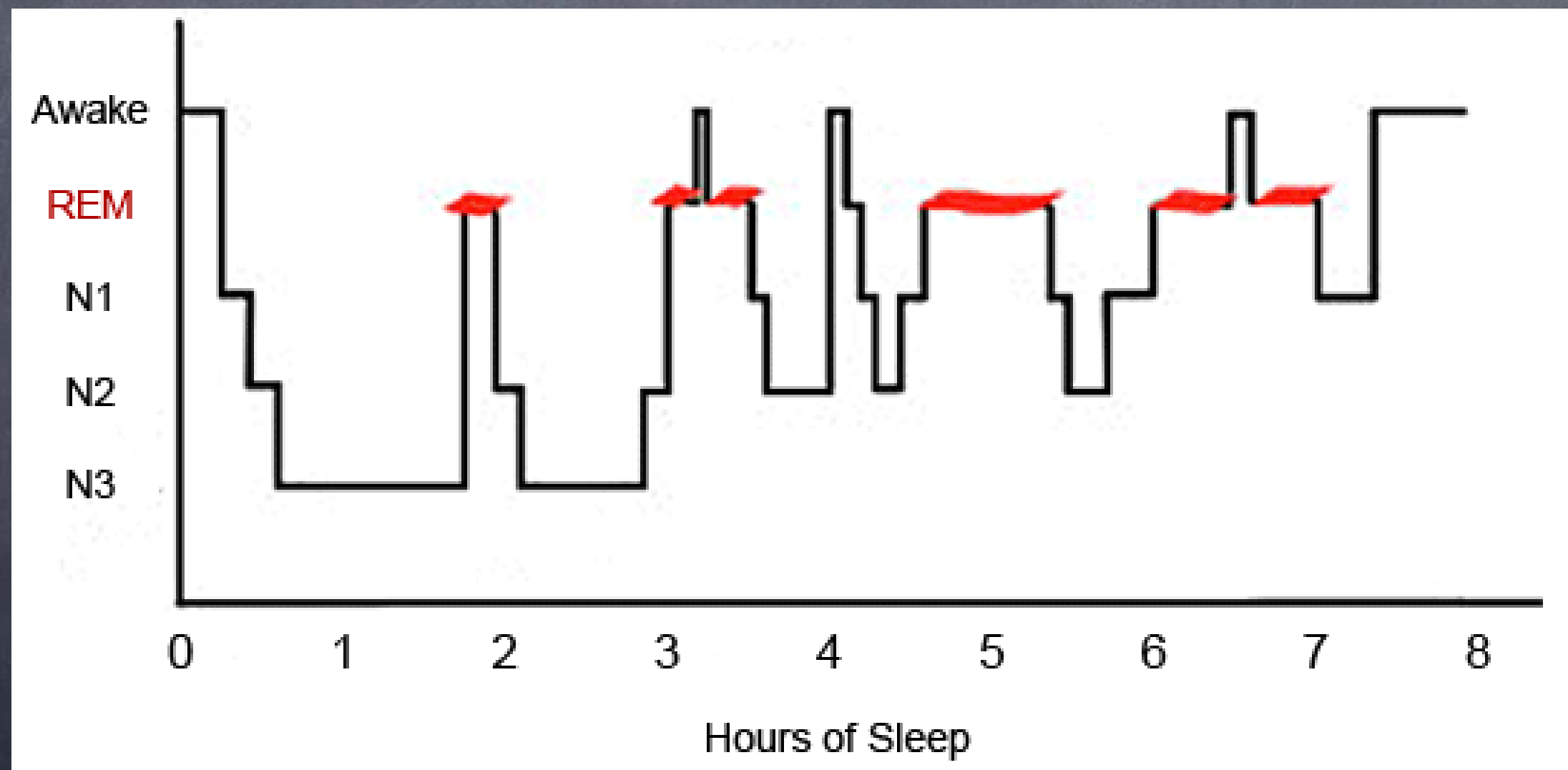
Discovery of REM

- Aserinsky and Kleitman, 1953
 - rapid eye movements during sleep
 - Fast (wake like) EEG activity



Nathaniel Kleitman
University of Chicago

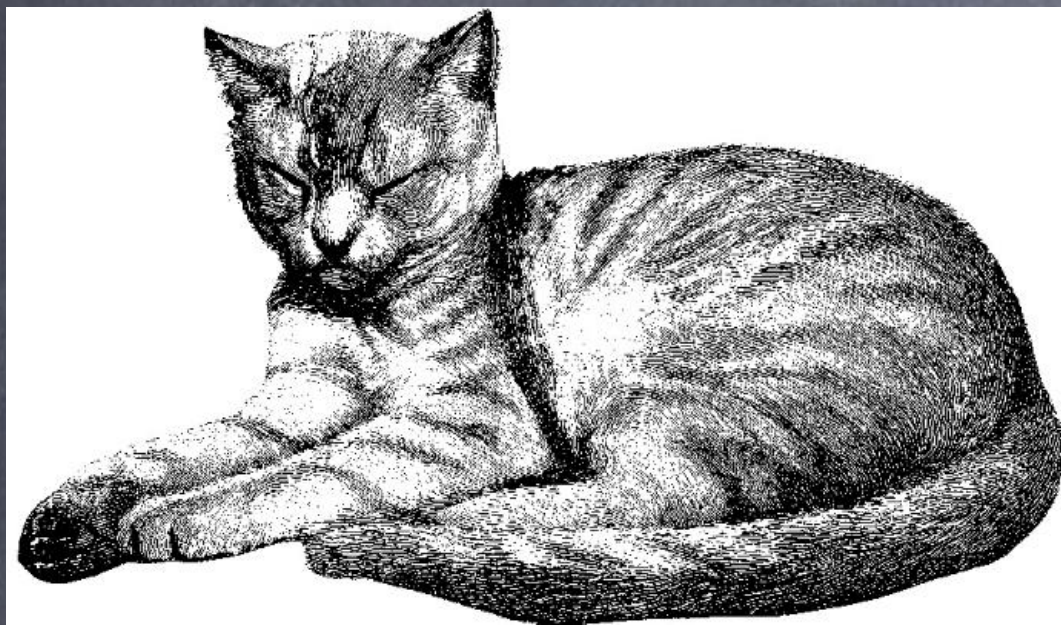
Sleep Stages



REM Features

- Low threshold for arousal
 - Very easy to wake up
 - Frequently describe vivid dreaming
- Highly activated amygdala
 - Increase in agitation, paranoia upon awakening
- Irregular HR
- Irregular tidal volume and RR
- Sexual arousal
- Drop in Body Temperature
 - Transient Ectothermia

Michel Juvet



REM Sleep

- Pontine lesions in cats caused a loss of REM atonia and the emergence of complex motor behaviors during REM sleep.



Feline Dream Enactment



Courtesy of Alon Avidan

REM sleep Behavior Disorder (RBD)



- Used with permission by Dr Carlos Schenck

RBD-Sleep Injury

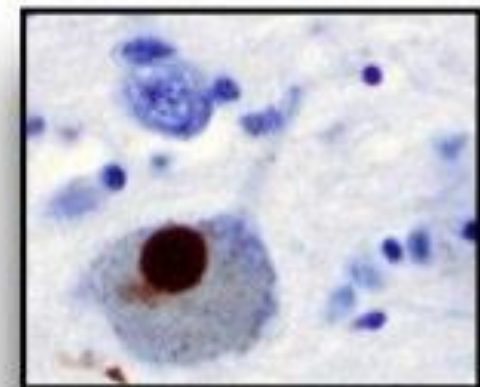


Minnesota Regional Sleep Disorders Center

REM Sleep Behavior Disorder

RBD is most commonly associated with neurodegenerative disease, particularly α -Synucleinopathies:

- Parkinson's disease
- Dementia with Lewy Bodies
- Multiple System Atrophy



Alpha-Synuclein staining of a Lewy body in a patient with Parkinson's disease.

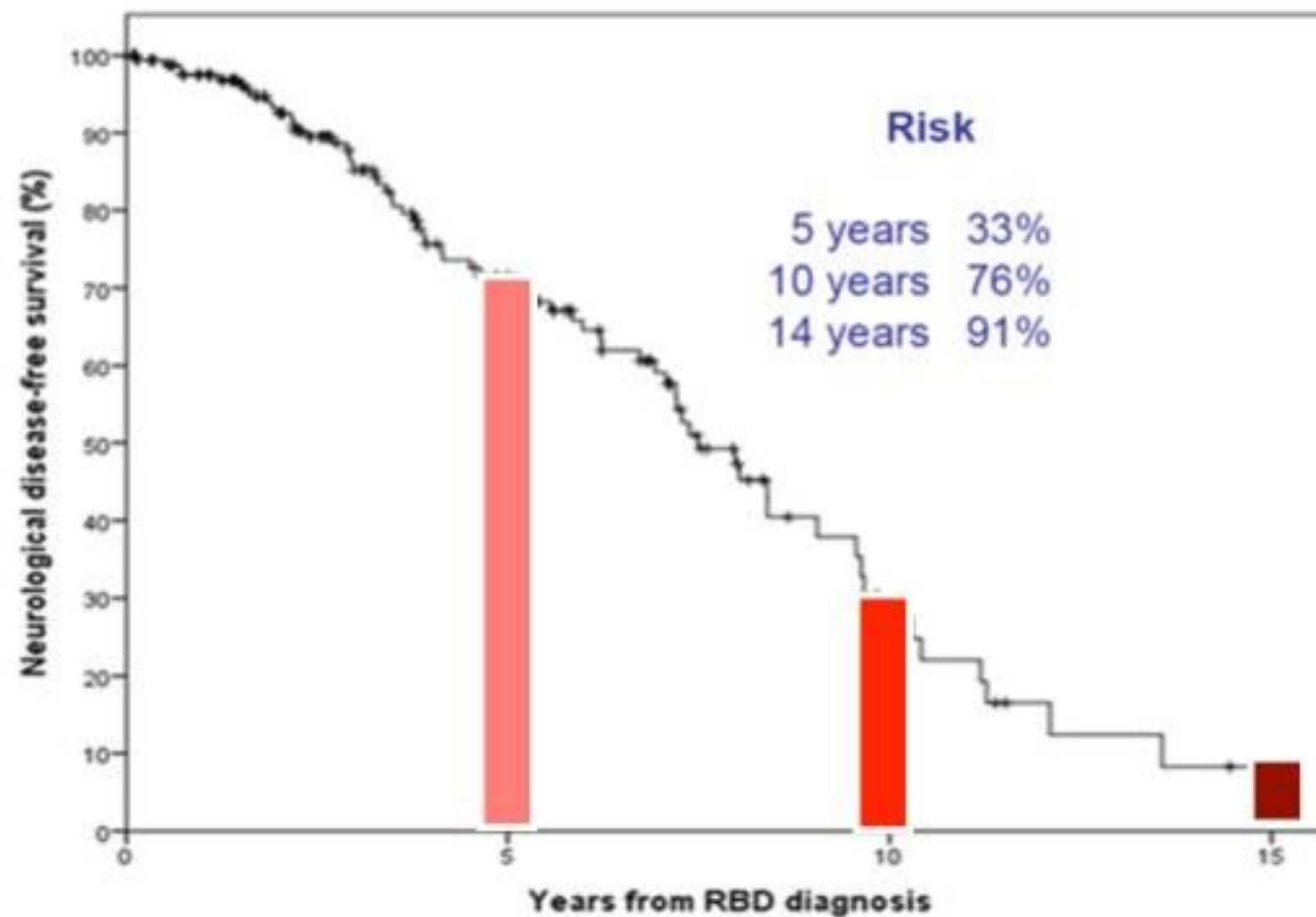
Neurological Features of RBD

- Early alpha-synuclein pathology.
 - Motor: bradykinesia, resting tremor, cogwheel rigidity
 - Non-Motor: hyposmia, constipation, orthostasis
 - Visuospatial dysfunction: impaired facial and color recognition, visual hallucinations



(Charcot 1879)

RBD Rates of Phenoconversion



Number of
patients at risk 174

65

10

0

Barcelona Group
Iranzo A, Fernandez-Arcos A, Tolosa E et al, PLOS ONE
2014;9:e89741

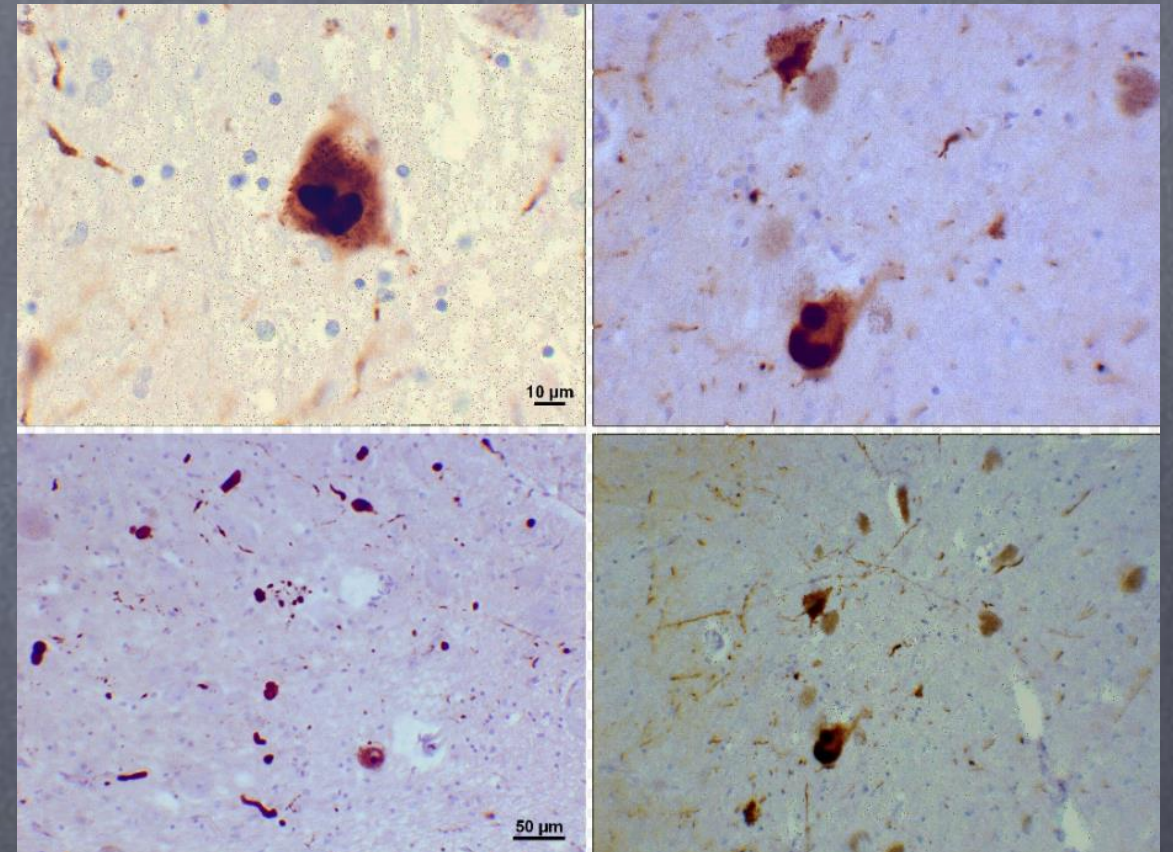
TABLE 1. LRs of risk and prodromal markers

	LR ⁺	LR ⁻
Risk markers		
Male sex	1.2 (male)	0.8 (female)
Regular pesticide exposure	1.5	n/a
Occupational solvent exposure	1.5	n/a
Nonuse of caffeine	1.35	0.88
Smoking		
Current	n/a	0.45
Never	1.25	n/a
Former	n/a	0.8
Sibling had PD with age onset <50	7.5	n/a
or		
Any other first-degree relative with PD	2.5	n/a
or		
Known gene mutation	see Supporting Table II	n/a
SN hyperechogenicity	4.7	0.45
Prodromal markers		
PSG-proven RBD	130	0.62
or		
Positive RBD screen questionnaire with >80% specificity	2.3	0.76
Dopaminergic PET/SPECT clearly abnormal (e.g., <65% normal, 2 SDs below mean)	40	0.65
Possible subthreshold parkinsonism (UPDRS >3 excluding action tremor)	10	0.70
or		
Abnormal quantitative motor testing	3.5	0.60
Olfactory loss	4.0	0.43
Constipation	2.2	0.80
Excessive daytime somnolence	2.2	0.88
Symptomatic hypotension	2.1	0.87
Severe erectile dysfunction	2.0	0.90
Urinary dysfunction	1.9	0.90
Depression (\pm anxiety)	1.8	0.85

From Berg et al 2015

Dream Enactment and MCI

- A history of Dream Enactment in the setting of MCI predicts Lewy Body Type Dementia over Alzheimer's disease upon post mortem examination.



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(Boeve 2001, Boeve 2010)

RBD indicates more aggressive disease

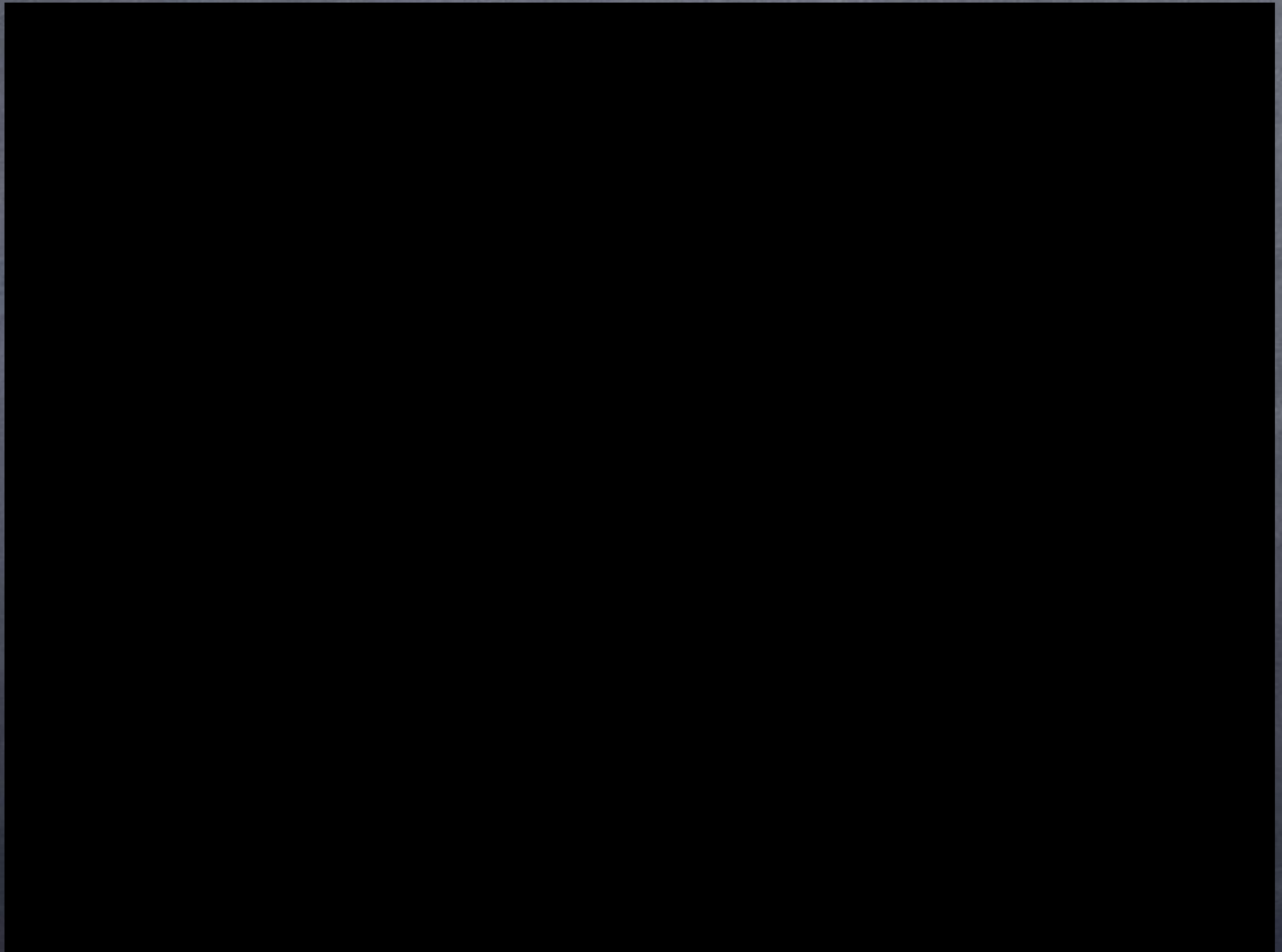
- PD + RBD patients (about 40% of PD patients) are more likely to have:
 - Higher Hoehn and Yahr, Greater motor fluctuations
 - More cognitive decline, hallucinations, autonomic instability, gait freezing, postural instability



(Charcot 1879)

(Romenets et al 2012, Videnovic et al 2013, Boeve et al 2013, Howell 2015)

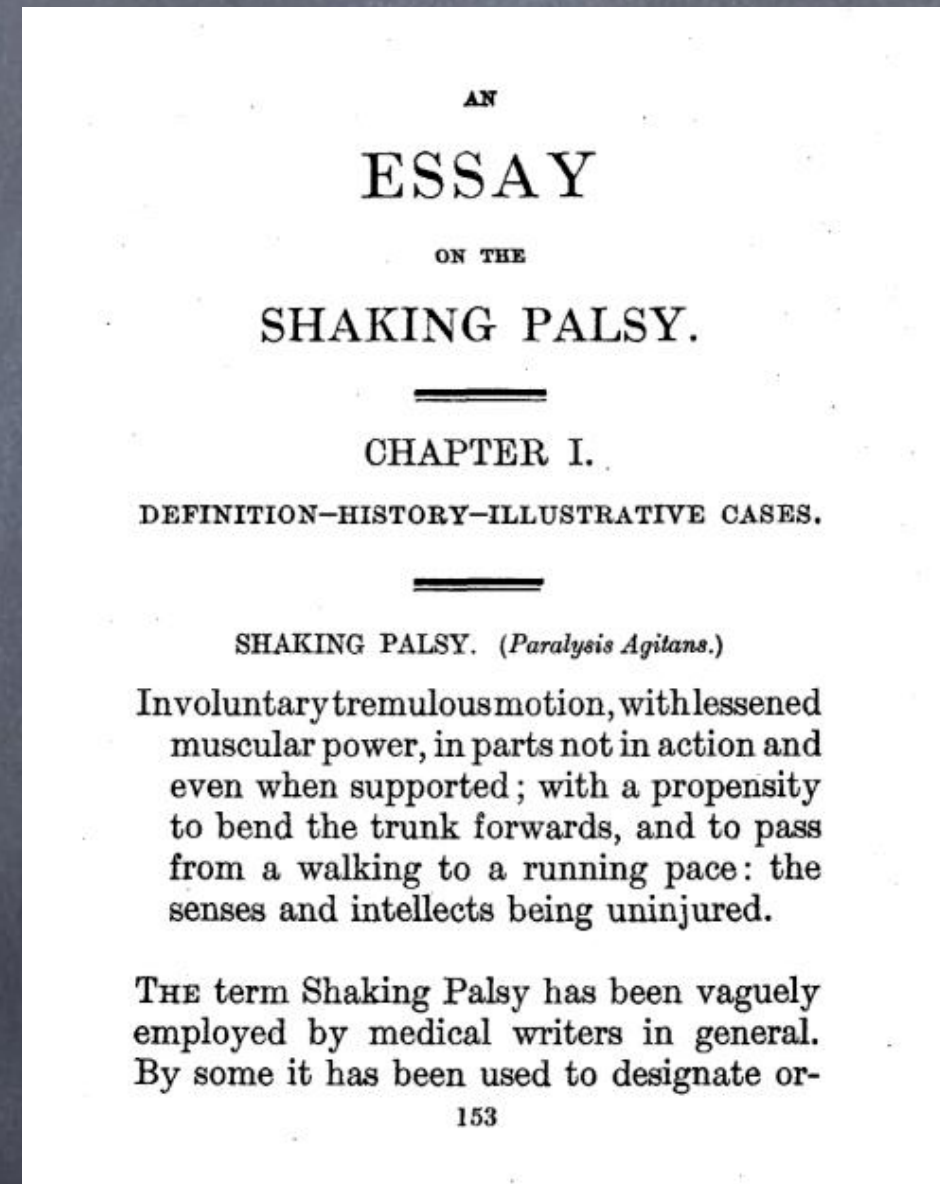
Freezing of Gait (FOG)



Paralysis Agitans

- Described by James Parkinsons in 1817
- Combination of tremor and bradykinesia
- Noted frequent sleep disruption

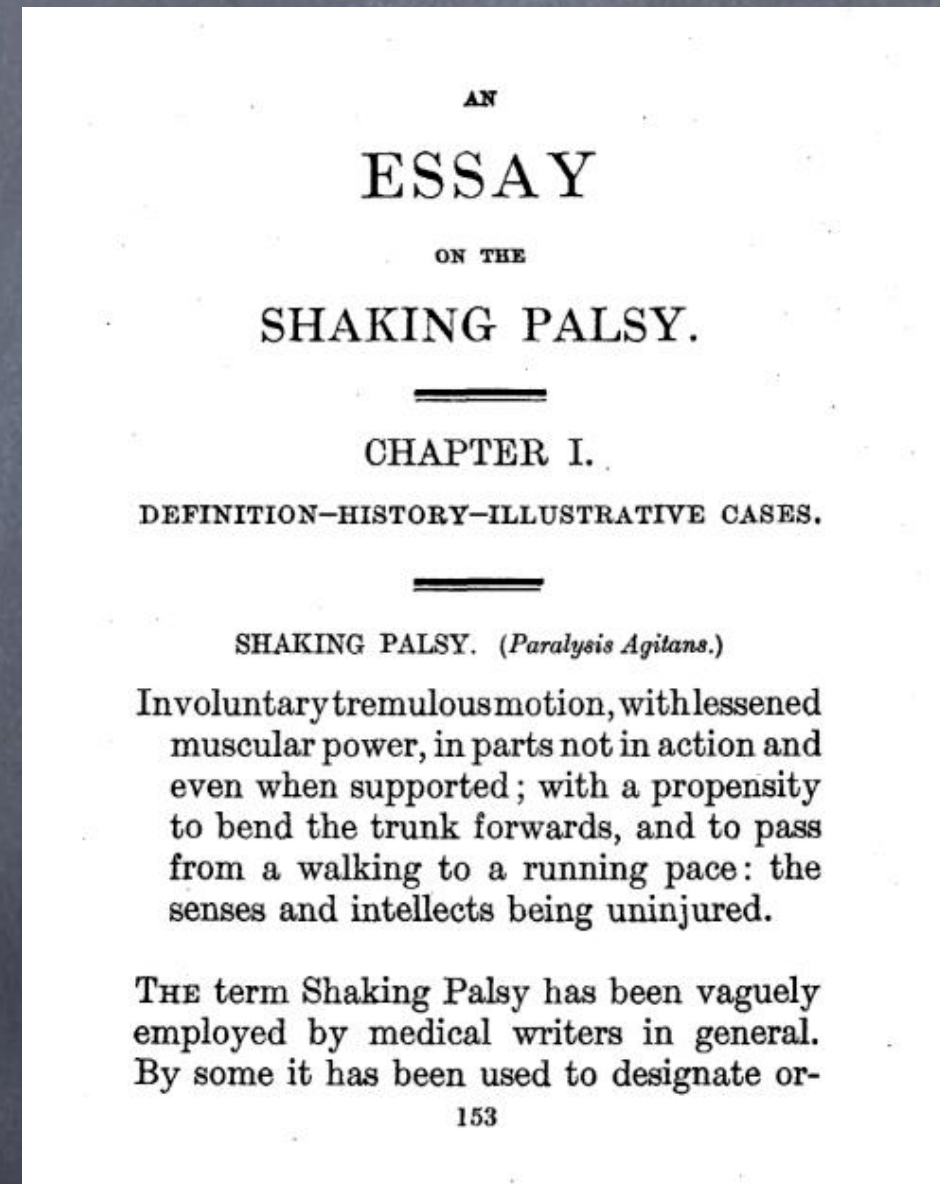
(Parkinson 1817)



“Sleep becomes much Disturbed”

- Case VI
- *“...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”*

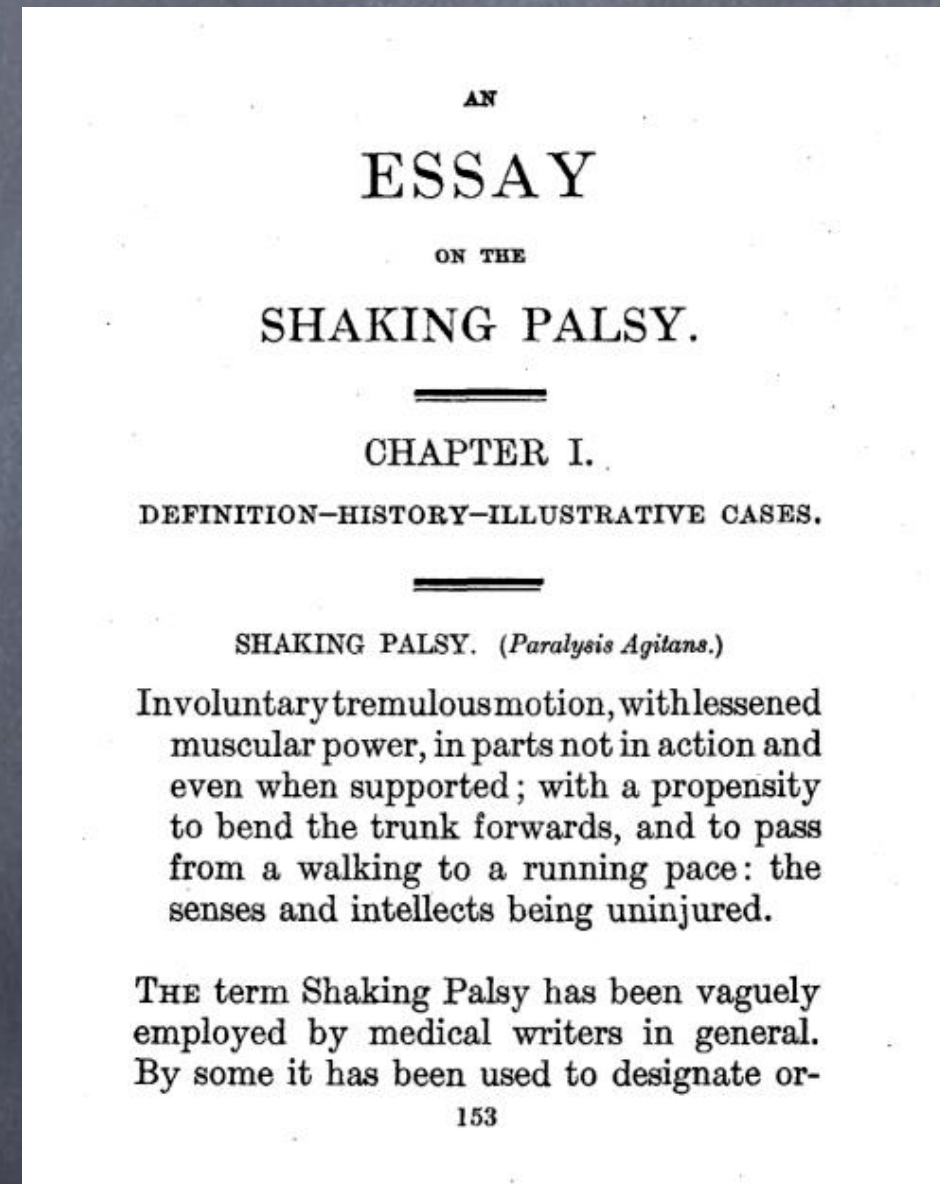
(Parkinson 1817)



“Sleep becomes much Disturbed”

- Case VI
- *“...when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room.”*

(Parkinson 1817)



RBD and Gait Freezing

The following is from the same case (Case VI) who had a evidence of violent dream enactment.

“...if whilst walking he felt much apprehension from the difficulty of raising his feet, if he saw a rising pebble in his path? He avowed, in a strong manner, his alarm on such occasions; and it was observed by his wife, that she believed that in walking across the room, he would consider as a difficulty the having to step over a pin.”

James Parkinson 1817

Neuroprotection

- International REM Sleep Behavior Study Group (IRBD SG) meets annually in the fall.
- Ultimate goal of the IRBD SG is to develop disease modifying treatments that slow, halt or reverse Parkinson's disease and other disorders of alpha-synuclein degeneration.

Canine dream enactment



Thank You



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