REM Sleep Behavior Disorder and Implications for Neurodegeneration

Joyce K. Lee-Iannotti, MD

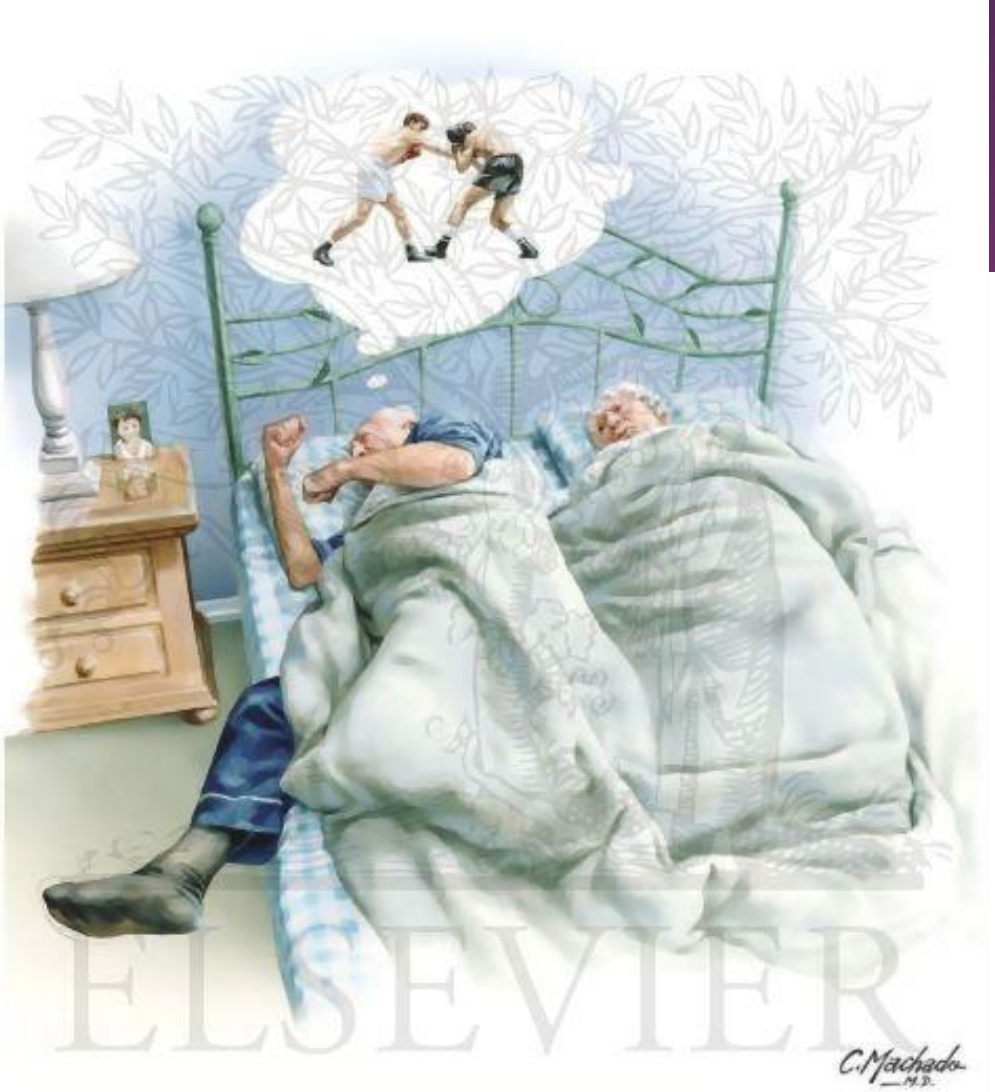
13th Annual Scientific Conference
Maryland Sleep Society
Saturday, October 28
10:45-11:45 am

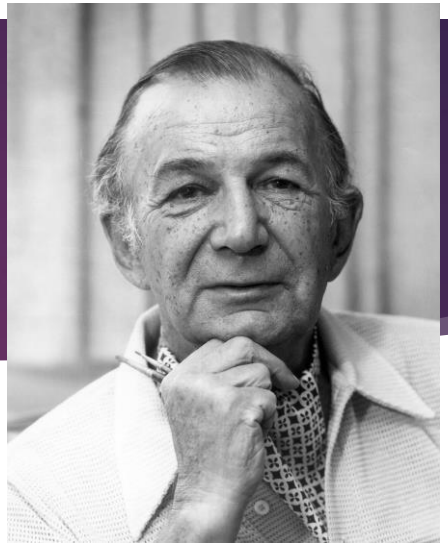
Disclosures

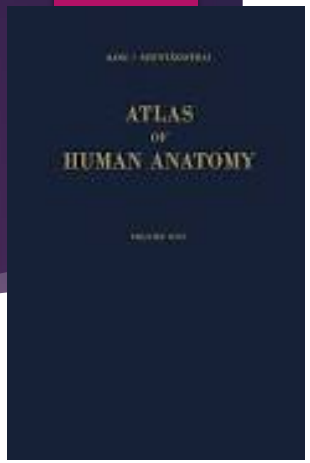
- **No COI**
- **I will be discussing "off-label" use of the following medications:**
  - **Melatonin**
  - **Clonazepam**
  - **Gabapentin**

Objectives

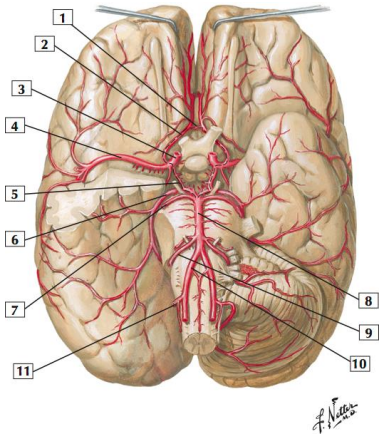
- **Describe the pathophysiology associated with REM Sleep Behavior Disorder (RBD)**
- **Discuss methods to diagnose and manage REM Sleep Behavior Disorder**
- **Review the current literature regarding future implications of RBD including development of Parkinson's disease**







Frank H. Netter, MD
1906-1991
American surgeon and medical illustrator



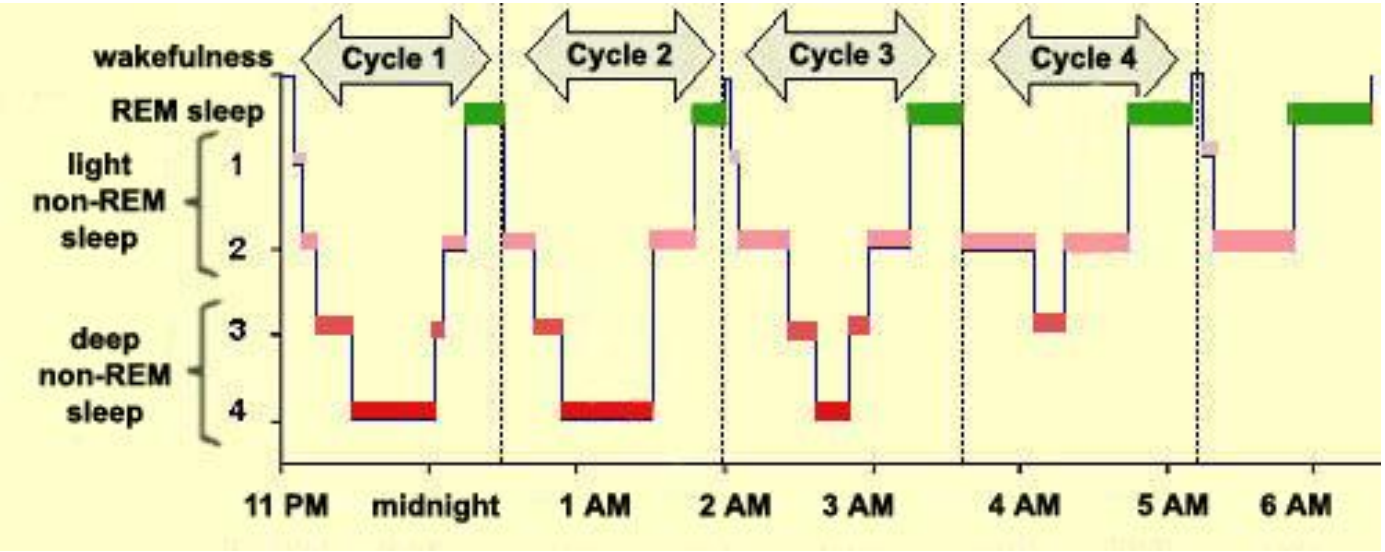
ICSD-3 (AASM)

	ICSD II (2005)	ICSD III (2014)
NREM Parasomnias	**Confusional Arousals** **Sleepwalking** **Sleep Terrors**	**Disorders of Arousal** **Confusional Arousals** **Sleepwalking** **Sleep Terrors** **Sleep Related Eating Disorder**
REM Parasomnias	**RBD** Recurrent Isolated Sleep Paralysis Nightmare Disorder	**RBD** Recurrent Isolated Sleep Paralysis Nightmare Disorder
Other Parasomnias	**Sleep Related Eating Disorder** Sleep Related Dissociative Disorder Sleep Enuresis Sleep Related Groaning (Catathrenia) Exploding Head Syndrome Sleep Related Hallucinations	Sleep Related Dissociative Disorder Sleep Enuresis Exploding Head Syndrome Sleep Related Hallucinations
Isolated Symptoms and Normal Variants		**Sleep Talking**

Bold Text

1st ½ of the Night → Non-REM Parasomnias

2nd ½ of the Night → REM Parasomnias



Pearls:
NREM vs REM Parasomnias

	NREM parasomnia	RBD
Time of Night	Early	Late
Age	Young, (PD- Somnolence)	50's +
Family History	LOTS	Partial (via PD)
Eyes	Open	Closed
Walking	**Yes**	**No**
Talk back?	Yes	No (unless awake)
Interaction	**Full**	**Little (coincidence)**
Associated ND disease	Little (late stages?)	Synucleinopathy +++

Courtesy of R. Postuma

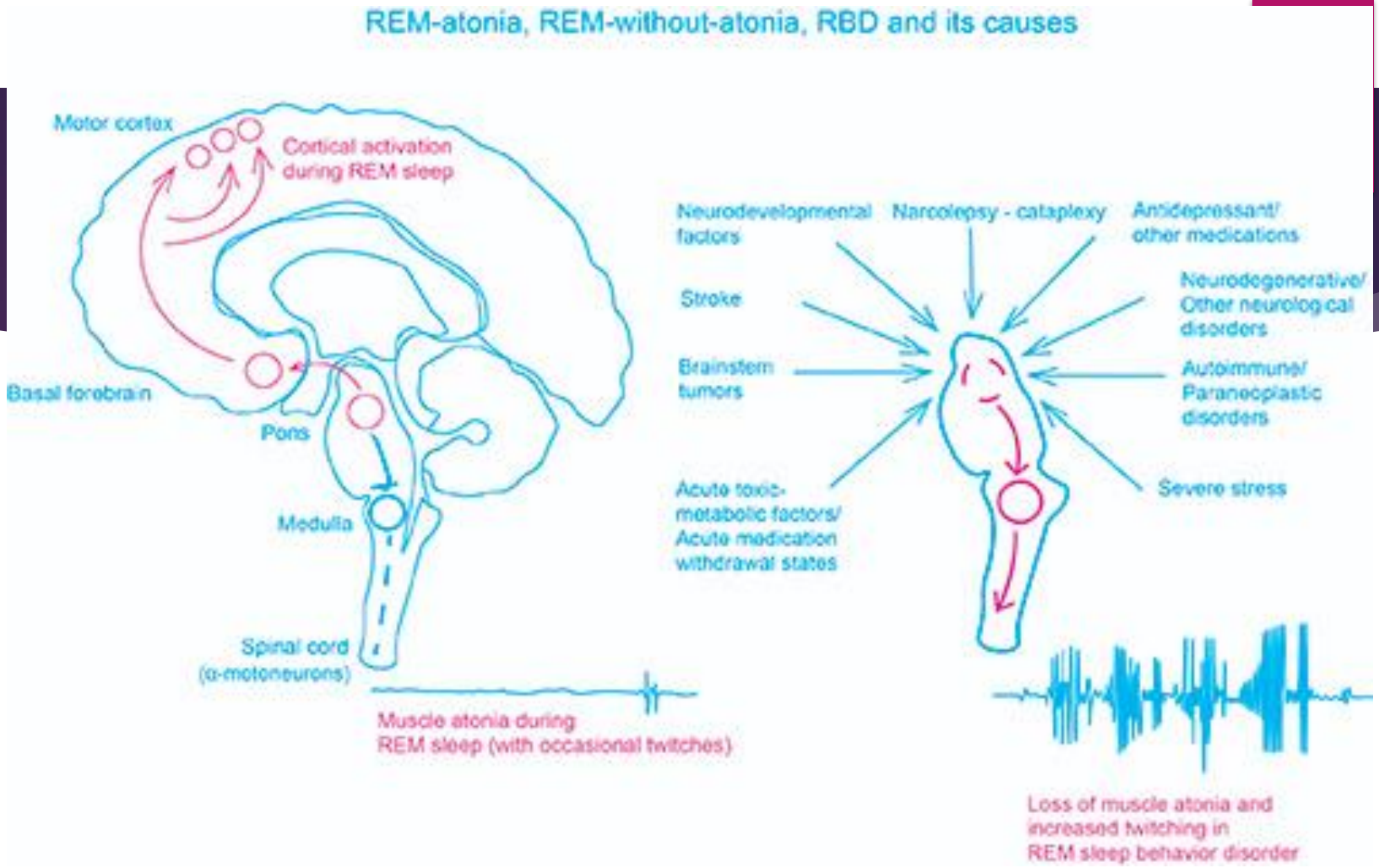
Side Note: Seizures Pearls

	NFLE Sleep-related hypermotor epilepsy (SHE)	Parasomnias
Duration	<2 minutes	>10 minutes
Timing	Events in the first 30 minutes	Events later in the night
Frequency	Multiple events per night	1-2 events/night
Complexity	Complex behavior uncommon	Often wandering and complex behavior
Semiology	Highly stereotyped, repetitive	Variable semiology
Recall	Often full recall of events and speech (exception: 2ndary generalization → no recall)	Event and speech recalled, not always

REM Sleep Behavior Disorder (RBD)

- **Dream-enactment behavior associated with loss of muscle atonia in REM sleep**

- **Tend to be violent → "Dr. Jekyl and Mr. Hyde Syndrome"**



The pons, the site for generating REM sleep, simultaneously sends ascending activating signals (in red) to the motor cortex and descending inhibitory signals (in blue) to the spinal cord alpha-motoneurons via the medulla, to result in REM atonia, with brief, benign twitches in REM sleep

Schenck et al, Sleep, 1986

REM Sleep Behavior Disorder (RBD)

- **Estimated prevalence 1% based on community-based epidemiological studies**
  - **Middle aged, older adults**
  - **Switzerland, Japan**
- **Highest prevalence amongst men >50 yo**
- **¼ of pts with PD experience RBD**

Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. *Sleep* 2017.

Sasai-Sakuma T, Takeuchi N, Asai Y, Inoue Y, Inoue Y. *Sleep* 2020.

RBD and non-tremor predominant PD

- **PD + RBD patients are more likely to manifest with non-tremor predominant PD**
- Freezing of gait (FOG)
- Postural instability
- Falls

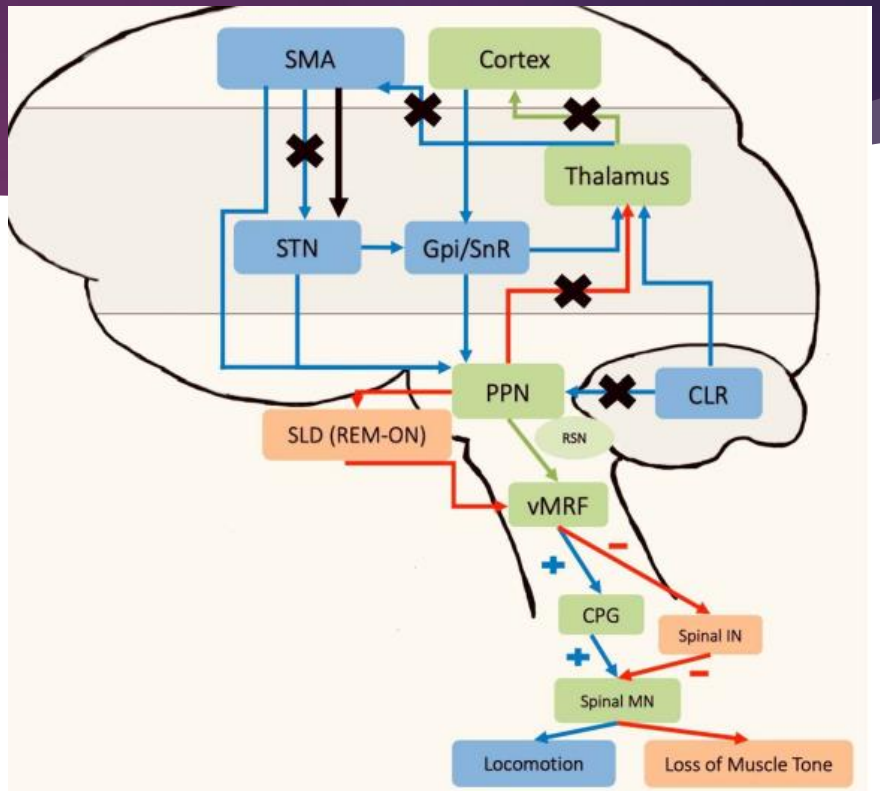


FIGURE 2: Changes in the neural networks seen in RBD and PD with FOG

Blue = motor locomotor region
Orange = REM sleep control
Green = overlap between MLR + REM
Black arrows = altered connection in RBD + PD with FOG

Nobleza et al. Cureus. 2020 Dec 30;12(12):e12385.

REM Sleep Behavior Disorder (RBD)

- **The minimum diagnostic criteria of RBD include movement of the body or limbs associated with dreaming and at least one of the following:**
  - **Potentially harmful sleep behavior**
  - **Dreams that appear to be acted out**
  - **Sleep behavior that disrupts sleep continuity**

    (Exp. Punching/ hitting spouse, running into walls, jumping out of windows)

ICD Criteria for RBD

TABLE 5-1 ***International Classification of Sleep Disorders, Third Edition*, Diagnostic Criteria for Rapid Eye Movement Sleep Behavior Disorder**[a]

All criteria of the following must be met for a diagnosis of rapid eye movement (REM) sleep behavior disorder

A. Repeated episodes of sleep-related vocalization and/or complex motor behaviors

B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep

RSWA

C. Polysomnographic recording demonstrates REM sleep without atonia

D. The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use

[a] Reprinted with permission from the American Academy of Sleep Medicine.[4]

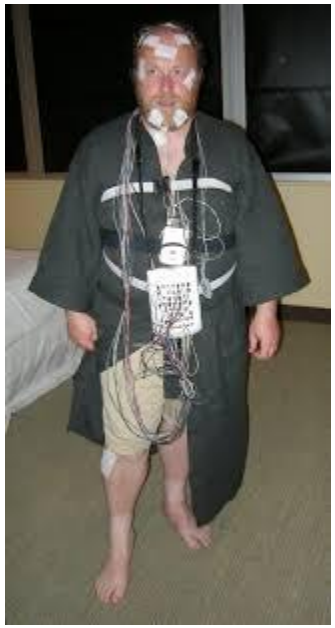
RBD is the only parasomnia that requires a PSG!

RBD1Q One question Screening Tool

- **Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?"**

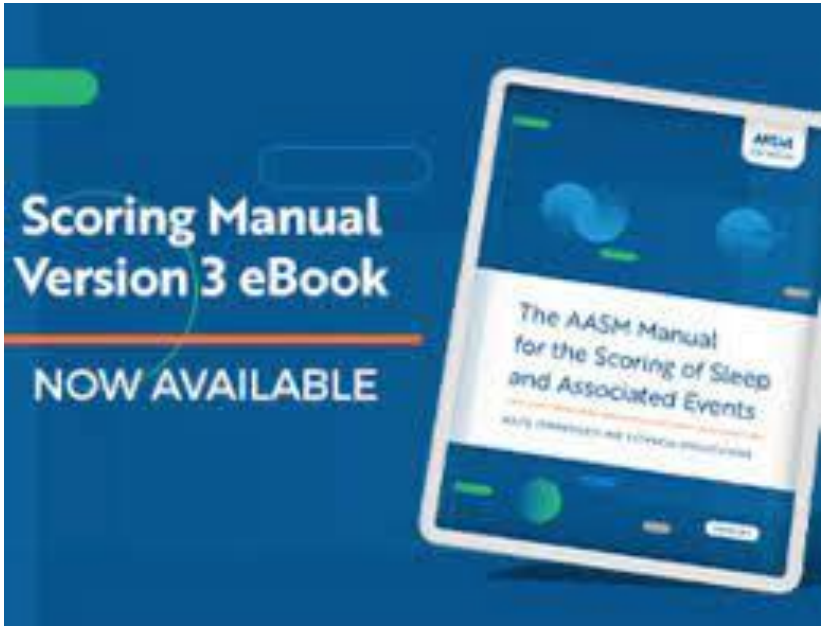
Postuma et al, Mov Disord, 2012.

REM Sleep Behavior Disorder (RBD)



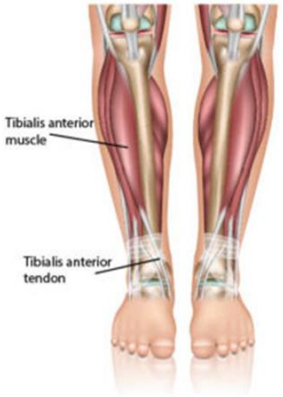
- **Diagnosis**
  - **Polysomnographic video recording is the most important diagnostic test in RBD**
  - **EEG, ECG, nasal flow, multiple electromyography channels**
  - **RBD PROTOCOL – extra limb leads**
    - **Legs ➔ anterior tibialis x 2**
    - **Arms ➔ Flexor digitorum superficialis x 2**
    - **Video very important!**

RBD protocol



Released June 2023
Version 3
AASM.org

RBD protocol



A. Technical Specifications[N1]

1. For monitoring leg movements (LMs), surface electrodes should be placed longitudinally and symmetrically in the middle of the anterior tibialis muscle so that they are 2–3 cm apart or 1/3 of the length of the anterior tibialis muscle, whichever is shorter. Both legs should be monitored for the presence of the leg movements. Separate channels for each leg are strongly preferred. Combining electrodes from the 2 legs to give 1 recorded channel may suffice for some clinical settings, although it should be recognized that this strategy may reduce the number of detected LMs. (see Figure 1) RECOMMENDED

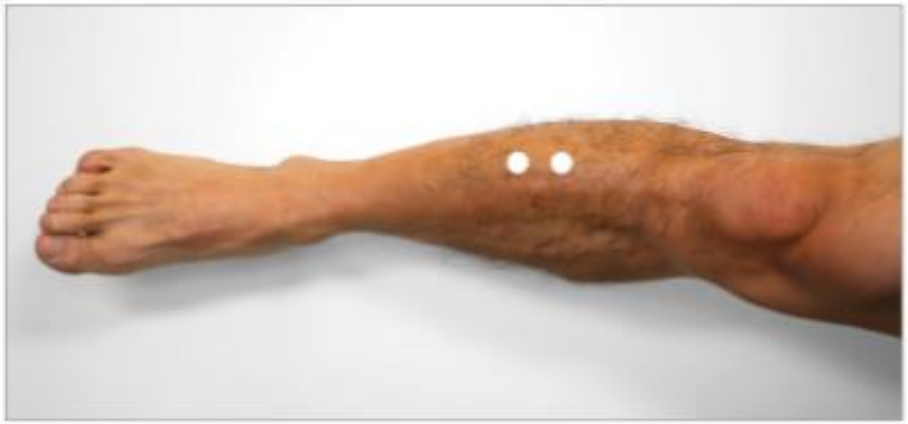


Figure 1. Placement of electrodes on the anterior tibialis muscle for monitoring leg movements. Illustration may not be to scale.

2. For monitoring leg movements, use of 60 Hz (notch) filters should be avoided. Impedances need to be less than 10,000 Ω. Less than 5,000 Ω is preferred but may be difficult to obtain. RECOMMENDED

RBD protocol

3. Movements of the upper limbs may be sampled using a similar method as for legs if clinically indicated. (see Figures 2 and 3) OPTIONAL

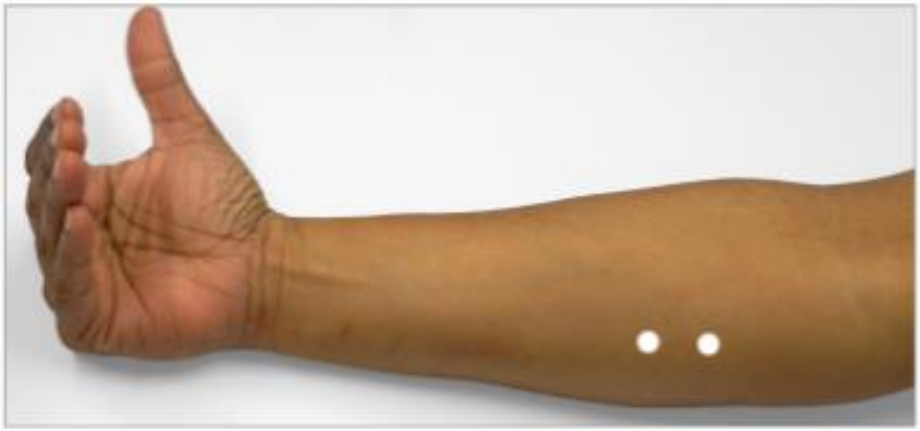


Figure 2. Placement of electrodes on the flexor digitorum superficialis for detecting transient muscle activity in REM sleep. Illustration may not be to scale.

Sinbar protocol (Sleep Innsbruck Barcelona)

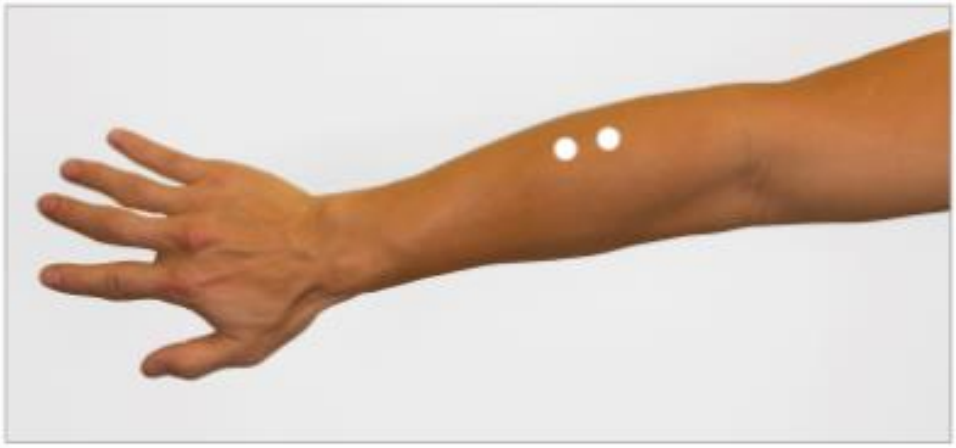
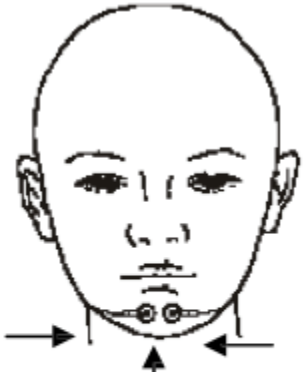


Figure 3. Placement of electrodes on the extensor digitorum communis for detecting transient muscle activity in REM sleep. Illustration may not be to scale.

RBD protocol

4. For detecting bruxism, in addition to the recommended placement of chin EMG electrodes as noted in the adult sleep staging rules chapter (IV.C), additional masseter electrodes may be placed if clinically indicated.[N2] (see Figure 4) OPTIONAL

Figure 4. Placement of electrodes on the masseter muscle for detecting bruxism. Illustration may not be to scale.



Two electrodes under the chin and one on the ledge of the chin

RBD protocol

5. **For detecting transient muscle activity in REM sleep, use one of the following EMG recordings:**[N3] OPTIONAL
   a. Flexor digitorum superficialis (see Figure 2)
   b. Extensor digitorum communis (see Figure 3)

6. **For diagnosis of RBD, time-synchronized, audio-equipped video PSG is essential to document complex motor behaviors and vocalizations during REM sleep. A diagnosis of RBD is based on demonstration of such episodes or a characteristic clinical history of dream enactment in addition to polysomnographic evidence of REM sleep without atonia.** RECOMMENDED

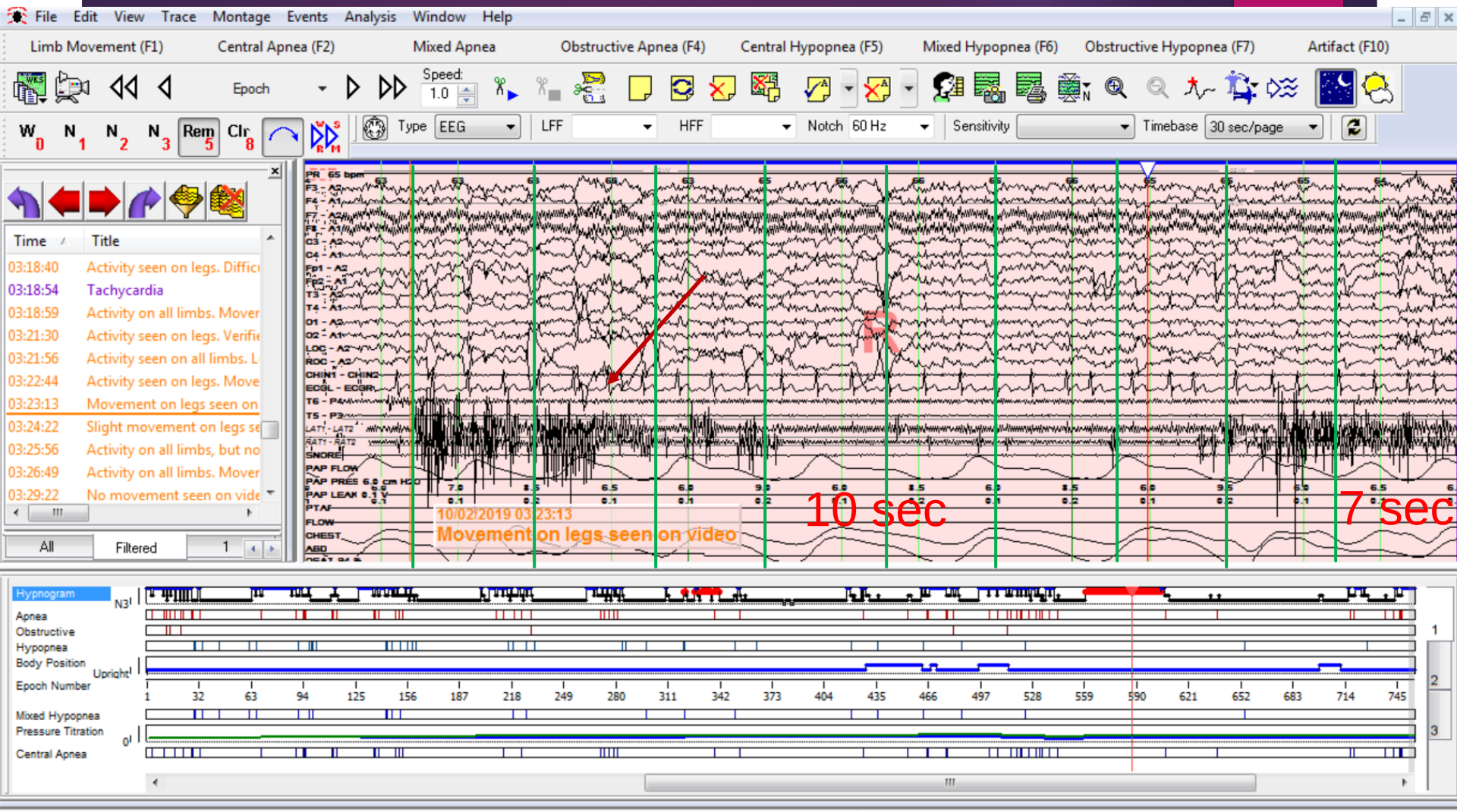
G. Scoring PSG Features of REM Sleep Behavior Disorder (RBD)

1. **Score in accordance with the following definitions:** RECOMMENDED

   Sustained muscle activity (tonic activity) in REM sleep: An epoch of REM sleep with at least 50% of the duration of the epoch having a chin EMG amplitude greater than the minimum amplitude demonstrated in NREM sleep.

   Excessive transient muscle activity (phasic activity) in REM sleep: In a 30-second epoch of REM sleep divided into 10 sequential 3-second mini-epochs, at least 5 (50%) of the mini-epochs contain bursts of transient muscle activity. In RBD, excessive transient muscle activity bursts are 0.1–5.0 seconds in duration and at least 4 times as high in amplitude as the background EMG activity.

2. **The polysomnographic characteristics of RBD are characterized by EITHER or BOTH of the following features:**[N1,N2,N3] RECOMMENDED
   a. Sustained muscle activity in REM sleep in the chin EMG
   b. Excessive transient muscle activity during REM in the chin or limb EMG


File Edit View Trace Montage Events Analysis Window Help
Limb Movement (F1)
Central Apnea (F2)
Mixed Apnea
Obstructive Apnea (F4)
Central Hypopnea (F5)
Mixed Hypopnea (F6)
Obstructive Hypopnea (F7)
Artifact (F10)
Epoch
Speed:
1.0
W N1 N2 N3 Rem Clr
Type EEG
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HFF
Notch 60 Hz
Sensitivity
Timebase 30 sec/page
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03:18:54 Tachycardia
03:18:59 Activity on all limbs. Mover
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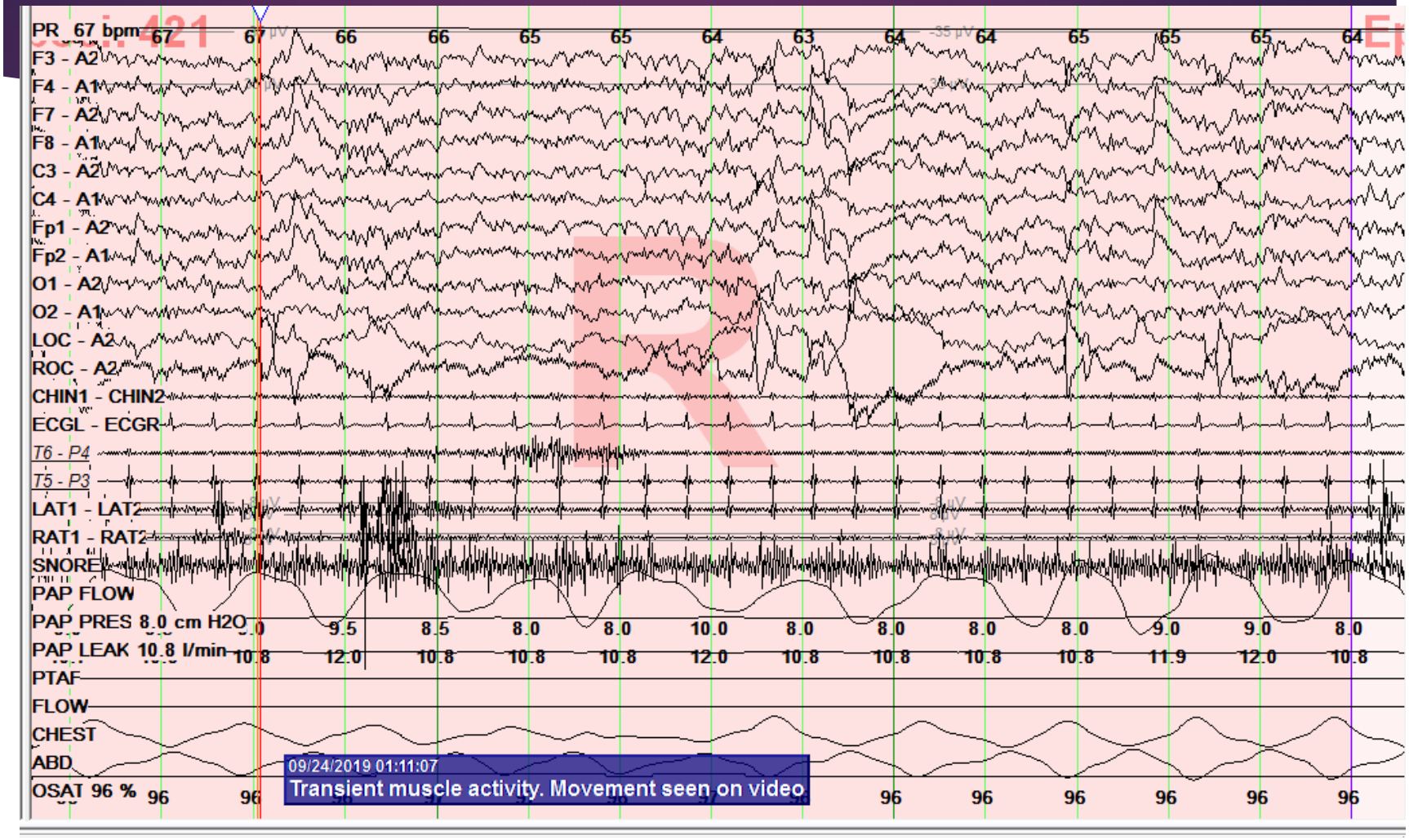
03:21:56 Activity seen on all limbs. L
03:22:44 Activity seen on legs. Move
03:23:13 Movement on legs seen on
03:24:22 Slight movement on legs se
03:25:56 Activity on all limbs, but no
03:26:49 Activity on all limbs. Mover
03:29:22 No movement seen on vide
All
Filtered
10/02/2019 03:23:13
Movement on legs seen on video
10 sec
7 sec
Hypnogram
Apnea
Obstructive
Hypopnea
Body Position
Upright
Epoch Number
Mixed Hypopnea
Pressure Titration
Central Apnea

Transient muscle activity (TMA)



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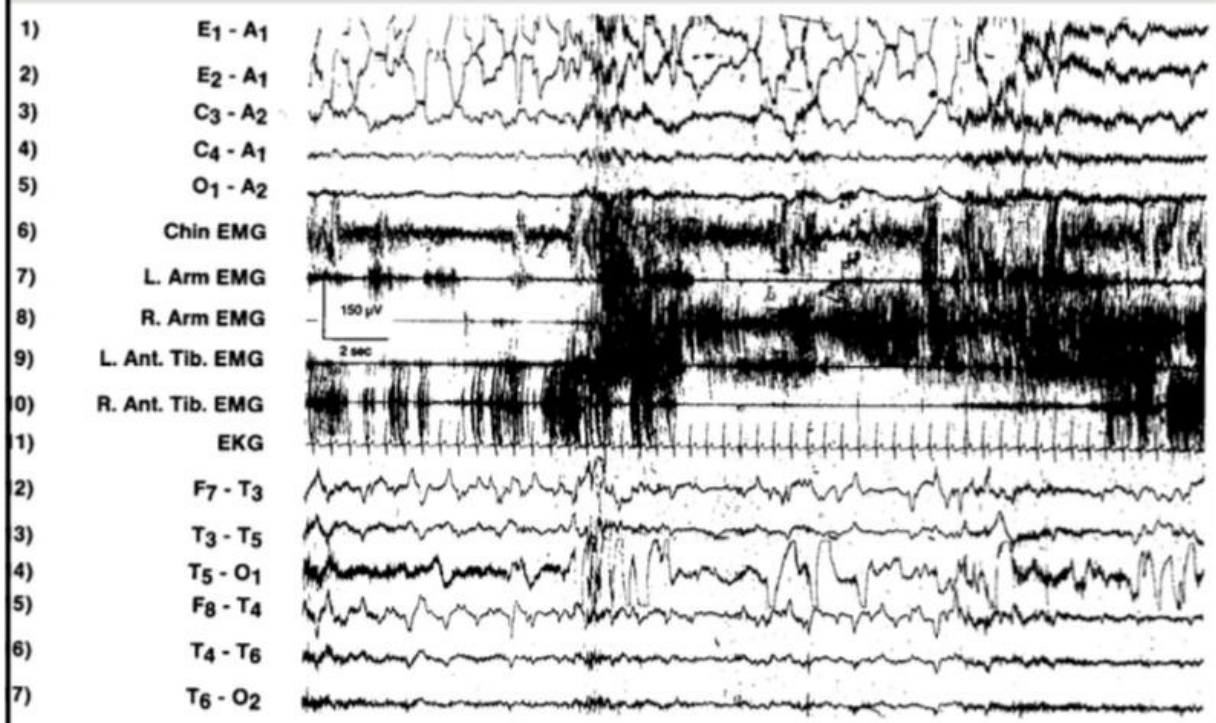
International Parkinson and Movement Disorder Society

RBD Polysomnogram



Key – NOT the dream

- loss of REM atonia

- ok from chin
  - ↑ sens if arms too

- Overall 90% sensitive in one night

Courtesy R. Postuma

http://dx.doi.org/10.5665/sleep.1886

Normative EMG Values during REM Sleep for the Diagnosis of REM Sleep Behavior Disorder

Birgit Frauscher, MD*[1]; Alex Iranzo, MD*[2]; Carles Gaig, MD[2]; Viola Gschliesser, MD[1]; Marc Guaita, MD[2]; Verena Raffelseder, MD[1]; Laura Ehrmann, MD[1]; Nuria Sola, MD[2]; Manel Salamero, PhD[3]; Eduardo Tolosa, MD[2]; Werner Poewe, MD[1]; Joan Santamaria, MD[2]; Birgit Högl, MD[1]; for the SINBAR (Sleep Innsbruck Barcelona) Group

*Drs. Frauscher and Iranzo contributed equally to this work.

[1]Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; [2]Neurology Service, Hospital Clinic de Barcelona, IDIBAPS, CIBERNED, Barcelona, Spain; [3]Psychology Service, Hospital Clinic de Barcelona, Barcelona, Spain

18% mentalis, 32% MM +FDS

Background: Correct diagnosis of rapid eye movement sleep behavior disorder (RBD) is important because it can be the first manifestation of a neurodegenerative disease, it may lead to serious injury, and it is a well-treatable disorder. We evaluated the electromyographic (EMG) activity in the Sleep Innsbruck Barcelona (SINBAR) montage (mentalis, flexor digitorum superficialis, extensor digitorum brevis) and other muscles to obtain normative values for the correct diagnosis of RBD for clinical practice.

Setting: Two university hospital sleep disorder centers.

Participants: Thirty RBD patients (15 idiopathic [iRBD], 15 with Parkinson disease [PD]) and 30 matched controls recruited from patients with effectively treated sleep related breathing disorders.

Interventions: Not applicable.

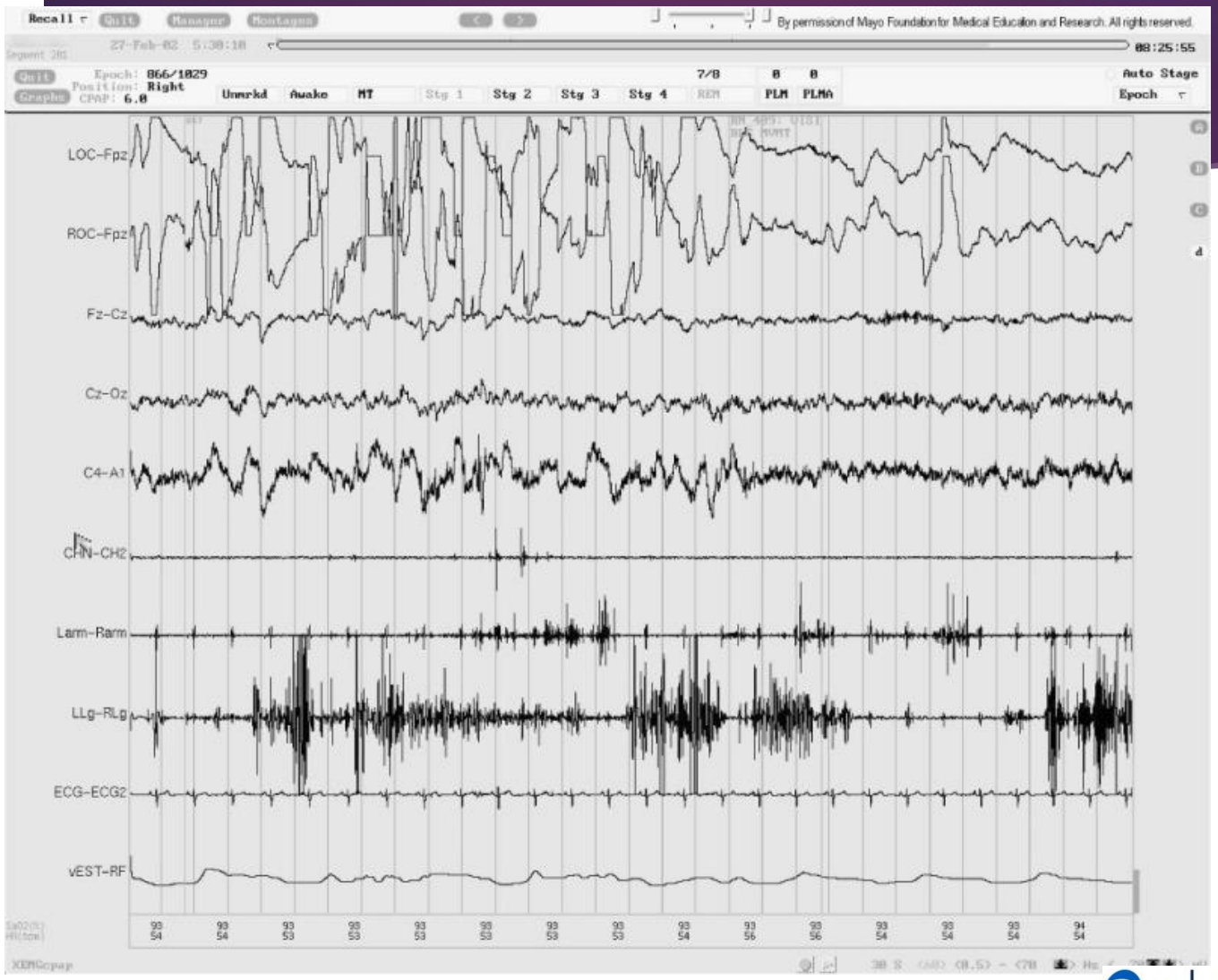
Methods and Results: Participants underwent video-polysomnography, including registration of 11 body muscles. Tonic, phasic, and "any" (any type of EMG activity, irrespective of whether it consisted of tonic, phasic or a combination of both) EMG activity was blindly quantified for each muscle. When choosing a specificity of 100%, the 3-sec miniepoch cutoff for a diagnosis of RBD was 18% for "any" EMG activity in the mentalis muscle (area under the curve [AUC] 0.990). Discriminative power was higher in upper limb (100% specificity, AUC 0.987–9.997) than in lower limb muscles (100% specificity, AUC 0.813–0.852). The combination of "any" EMG activity in the mentalis muscle with both phasic flexor digitorum superficialis muscles yielded a cutoff of 32% (AUC 0.998) for patients with iRBD and with PD-RBD.

Conclusion: For the diagnosis of iRBD and RBD associated with PD, we recommend a polysomnographic montage quantifying "any" (any type of EMG activity, irrespective of whether it consisted of tonic, phasic or a combination of both) EMG activity in the mentalis muscle and phasic EMG activity in the right and left flexor digitorum superficialis muscles in the upper limbs with a cutoff of 32%, when using 3-sec miniepochs.

Keywords: SINBAR EMG montage, normal values, cutoff, EMG activity, quantification, movement disorders

Citation: Frauscher B; Iranzo A; Gaig C; Gschliesser V; Guaita M; Raffelseder V; Ehrmann L; Sola N; Salamero M; Tolosa E; Poewe W; Santamaria J; Högl B. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. *SLEEP* 2012;35(6):835-847.

Example epochs



Most common cause of iatrogenic RBD is medications – MAOI's, SSRI's, TCA's and SNRI's except buproprion.

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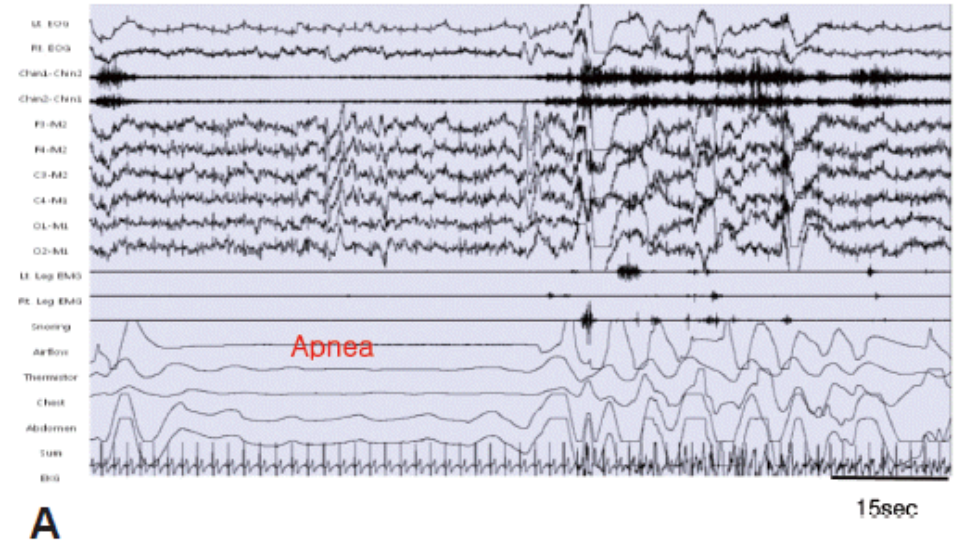
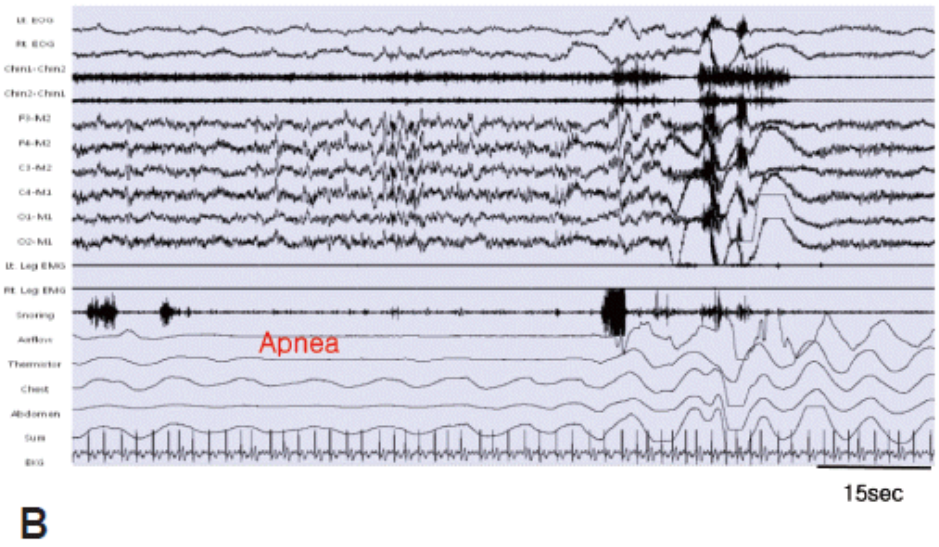
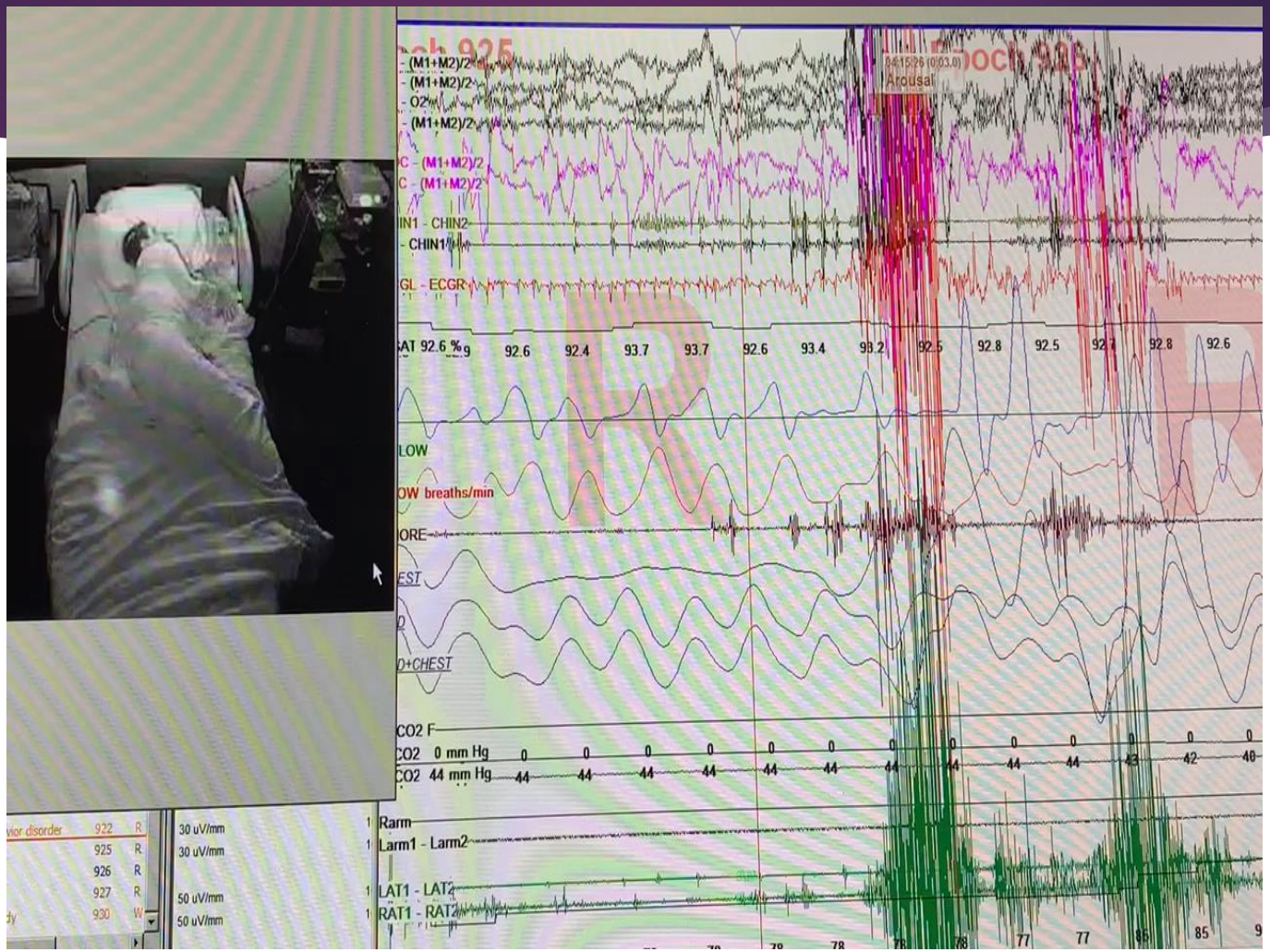
Pseudo-RBD due to SRBD





- **RBD can also be due to other sleep disorders including OSA and this scenario is termed as pseudo-RBD**
- **Usually resolves with optimal CPAP pressure**
- **Not associated with NDD if pseudo-RBD**

RBD Clip 1



Video used with consent and courtesy of Dr. Karin Johnson, MD
University of Massachusetts Medical School-Baystate

RBD Clip 2

Video used with consent and courtesy of Dr. Carlos Schenk MD University of Minnesota, https://youtu.be/rFXYRQ9xPUA

RBD Treatment

- **Clonazepam is effective in nearly 90% of patients but not always first line**
  - **0.5-2 mg qhs**
  - **SE's: sleepiness, falls, cognitive deficits, dependence/tolerance**
- **Melatonin may be effective – 3 mg (up to 12 mg)**
  - **Two small-scale studies – helped >80%**
  - **Recent RCT may be negative**
- **Off label: Gabapentin ("Vitamin G"), Rotigitine patch**
- **Other meds: imipramine, carbamazepine, DA agonists in PD pts (pramipexole, levodopa)**
- **Remove triggers -- antidepressants**
- **Symptoms will return once off the medication**

RBD Treatment

- **Educate the patient and bed partner about environmental safety**
  - **Remove dangerous objects from the room, mattress placed on floor, zip up patient in sleeping bag, bed rails, sleep alone**

Banner University Medicine

April 1, 2023

JCSM | Journal of Clinical Sleep Medicine

SPECIAL ARTICLES

Management of REM sleep behavior disorder: an American Academy of Sleep Medicine clinical practice guideline

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Howell et al, JCSM, April 2023

April 1, 2023

Table 2—Summary of recommended interventions in adult populations.

Intervention	Strength of Recommendation	Critical Outcomes Showing Clinically Significant Improvement*		
		RBD Symptoms	RBDQ Score† (behavioral)	RBD Frequency‡
Isolated RBD				
Clonazepam	Conditional for	✓	✓	
Melatonin (immediate-release)	Conditional for	✓		✓
Pramipexole	Conditional for	✓		✓
Rivastigmine	Conditional for			✓
Secondary RBD due to medical condition				
Clonazepam	Conditional for	✓		
Melatonin (immediate-release)	Conditional for	✓		✓
Rivastigmine	Conditional for			✓
DBS	Conditional against	X		
Drug-induced RBD				
Drug discontinuation	Conditional for	✓		

*✓ = critical outcomes showing clinically significant improvement. X = critical outcomes not showing clinically significant improvement. Blank cells = no reported data for this critical outcome. †RBDQ = RBD Questionnaire (includes Korean, Japanese, and Hong Kong versions). ‡RBD frequency = the rate of RBD symptoms over a period of time. DBS = deep brain stimulation, RBD = rapid eye movement sleep behavior disorder.

Howell et al, JCSM, April 2023

doi:10.1093/brain/awz030 BRAIN 2019: 142; 744–759 | 744

BRAIN
A JOURNAL OF NEUROLOGY

Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study

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See Morris and Weil (doi:10.1093/brain/awz014) for a scientific commentary on this article.

Postuma, Brain, 2019.

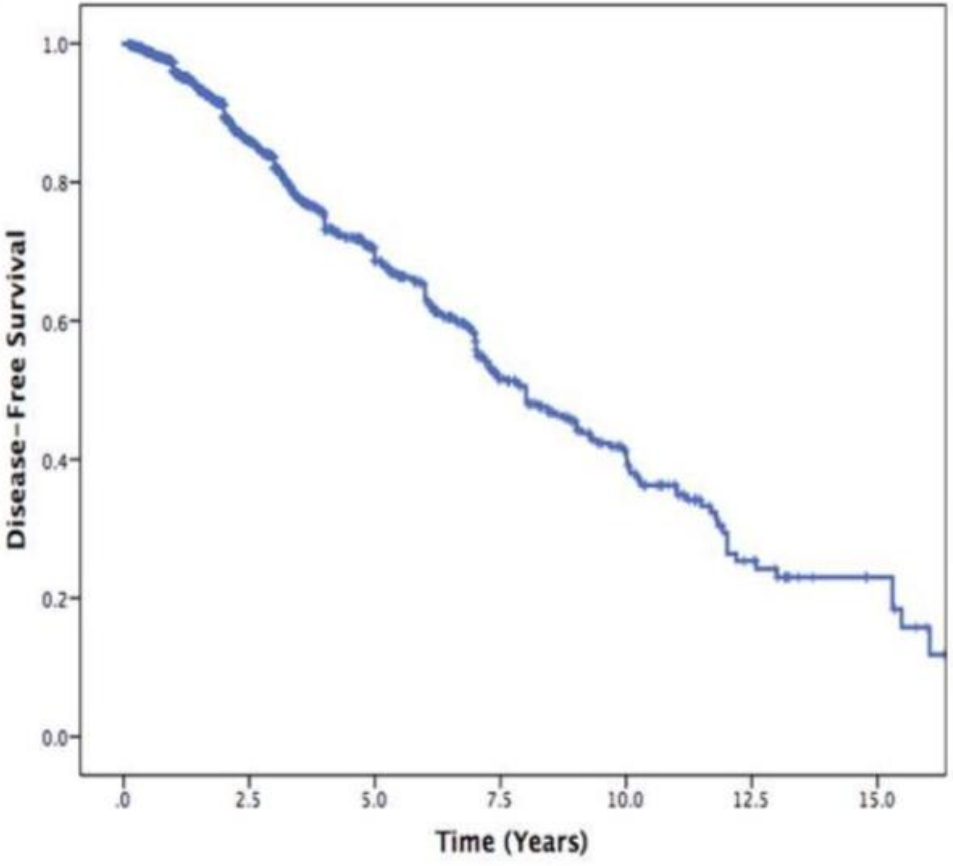
- Early studies showed a conversion rate of 80-90% within 1-2 decades to an a-synuclein state
  Iranzo, Lancet Neurol, 2016.

- 1280 pts followed for an average of 4.6 yrs (range 1-19 yrs) showing a conversion rate of 6.3%/year with 73.5% converting after a 12-year f/u

✓ Predictors: abnormal motor testing, olfactory deficit, MCI, ED, abnormal DAT, color vision abn, constipation, REM atonia loss, advanced age

International Parkinson and Movement Disorder Society

3. RBD can predict PD



Postuma, et al, Brain 2019

1280 patient study, 24 centers from IRBDSG

Overall: 6-7% / year

50% by 7.5 years

73% by 12 years

Half parkinsonism, half DLB

Bottom line:

PSG-proven RBD

= neurodegeneration

(synuclein every time)

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 (± anxiety)	1.8	0.85

n/a, not applicable.

Berg et al. Movement Disorders 2015. Oct;30(12):1600-11.

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Review

Biomarkers of conversion to α-synucleinopathy in isolated rapid-eye-movement sleep behaviour disorder

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Miglis, et al. Lancet Neuro 2021.

Biomarkers for pheno-conversion

	Subtype	Availability	Cost	Sensitivity and specificity	Remarks
Neurophysiology					
RSWA quantified by visual or automated methods (eg, SINBAR, rapid-eye-movement atonia index)	Diagnostic, prognostic, monitoring	High	Low	Diagnostic: 85–95% and 85–95%;[97-105] prognostic: 78–89% and 61–70%[5]	Robust data supporting both visual and automatic methods, with similar results despite differences in methods; few studies
Cyclic alternating pattern rate	Diagnostic, prognostic	Moderate	Moderate	NA	Only one study;[8] special analyses of EEG required
Biomarkers obtained through artificial intelligence, machine learning, and deep neural network-based methods	Diagnostic, prognostic, combined	Low	High	Diagnostic: 91–98% and 93–94%; prognostic: AUC 78%[9,10]	Few studies[9,10]

RSWA = the neurophysiological hallmark of RBD

- **One of the earliest signs of neurodegeneration**
- **May show progression of disease**

Miglis, et al. Lancet Neuro 2021. 20(8):671-684

Motor function	Lack specific protocols, appears later in the disease state				
Upper extremity alternate-tap test	Diagnostic, prognostic, monitoring, combined	High	Low	Year 0: 100% and 83%;[24] year −1: 92% and 86%; year −2: 88% and 89%; year −3: 91% and 86%	Easy to do; year 0=phenoconversion to PD or DLB; years −1, −2, −3=years before phenoconversion
Speech abnormalities quantified by means of acoustic analysis	Prognostic, monitoring	High	Low	67% and 71%[16]	Easy to do; only cross-sectional validation studies
Gait dysfunction by instrumental analysis	Prognostic, monitoring	Moderate	High	NA	Limited to few specialised centres; cross-sectional studies only
Wearable devices and smartphones	Prognostic, monitoring	High	Low	92% and 90%[18]	Cross-sectional validation studies only
Cognition	Seems to point more to DLB than PD				
Trail Making Test Part B	Diagnostic, prognostic, monitoring, combined	High	Low	Year 0: 100% and 83%;[24] year −1: 92% and 86%; year −2: 88% and 89%; year −3: 91% and 86%	Only one longitudinal study; early identification of prodromal DLB; year 0=phenoconversion to DLB; years −1, −2, −3=years before phenoconversion
Semantic verbal fluency	Monitoring, diagnostic, prognostic, combined	High	Low	Year 0: 91% and 97%;[24] year −1: 91% and 91%; year −2: 80% and 91%; year −3: 90% and 74%	Only one longitudinal study; cognitive change over time for prodromal DLB; year 0=phenoconversion to DLB; years −1, −2, −3=years before phenoconversion
Rey Auditory-Verbal Learning Test (immediate recall)	Diagnostic, prognostic, monitoring, combined	High	Low	Year 0: 92% and 89%;[24] year −1: 100% and 89%; year −2: 100% and 75%; year −3: 82% and 89%	Only one longitudinal study; cognitive change over time for prodromal DLB; year 0=phenoconversion to DLB; years −1, −2, −3=years prior to phenoconversion
Olfaction	Hyposomia = synuclein deposition in the olfactory bulbs				
Odour identification testing (eg, Sniffin' Sticks, UPSIT)	Diagnostic, prognostic, combined	High	Low	86–91% and 76–88%[106]	Easily done with conversion data between Sniffin and UPSIT available[107]
Ophthalmic function	Color discrimination = thinning of the retinal ganglion cells				
Farnsworth-Munsell 100-Hue test	Diagnostic, prognostic	Moderate	Low	NA	Easily done; limited data
Optical coherence tomography (structural imaging of the parafoveal avascular zone)	Diagnostic, prognostic	Low	Moderate	NA	Highly promising for investigating other pathways at risk of early degeneration

Executive function

Verbal episodic memory

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Biomarkers for pheno-conversion

	Subtype	Availability	Cost	Sensitivity and specificity	Remarks
(Continued from previous page)					
Autonomic function	Constipation, erectile dysfunction = greatest risk of phenoconversion, putaminal DA dysfxn, MSA				
Autonomic questionnaires	Diagnostic, prognostic, monitoring, combined	High	Low	NA	Easily done and can be easily repeated over time
Heart rate variability analysis	Diagnostic	High	Low	NA	Easily obtained from baseline vPSG; sensitive to artifact
Metaiodobenzylguanidine	Diagnostic	Moderate	Moderate	NA	Might help distinguish PD and DLB from MSA[51]
Cardiovascular reflex testing	Diagnostic, prognostic, monitoring, combined	Low	Moderate	NA	Limited to few specialised centres; might help distinguish PD and DLB from MSA[49]
Biofluids	RT-QuIC = real-time quaking-induced conversion, ID pathological alpha –synuclein deposition				
CSF RT-QuIC	Diagnostic, prognostic, monitoring	Low	Moderate	100% and 98%[55]	Somewhat invasive
Nasal swabs (olfactory mucosa) RT-QuIC	Diagnostic	Moderate	Moderate	44·4% and 90%[57]	Minimally invasive, ENT specialist needed for sampling
Serum neuronal exosomal α-synuclein	Diagnostic	Low	High	95% and 93%[59]	Most appealing serum marker sensitivity and specificity

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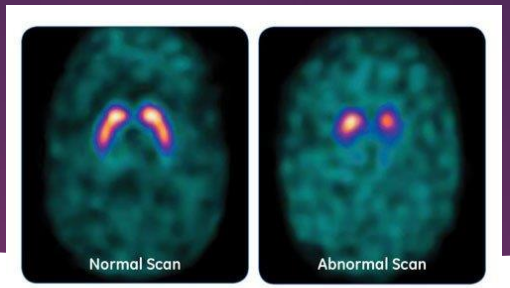

"Comma"-shaped
Possible essential tremor

"Period"-shaped
Possible parkinsonian syndrome

Neuroimaging					
^{123}I-FP SPECT (dopamine transporter SPECT)	Diagnostic, prognostic, monitoring, combined	Moderate	Moderate	29·3% and 100%[71]	Low diagnostic value in differentiating patients with isolated RBD from controls; high prognostic value in identifying future phenoconverters; low prognostic value in identifying phenoconversion subtype; responsive to dopamine-oriented therapy
^{18}F-FDG PET	Diagnostic, monitoring, combined	Moderate	Moderate	52·4% and 100%[67,73]	Moderate diagnostic value in differentiating patients with isolated RBD from controls; high diagnostic potential in predicting α-synucleinopathy subtype but requires independent validation; possible prognostic value has yet to be shown in large series; useful for monitoring disease progression; possibly responsive to therapy
MRI for nigrosome, MRI for substantia nigra neuromelanin, MRI for cortical thinning, and MRI for DBM	Diagnostic, prognostic, combined	Moderate	Moderate	MRI nigrosome: 27·5–77% and 97–92·3%;[74] MRI substantia nigra neuromelanin: 90% and 94%[108]	Good diagnostic potential in differentiating patients with isolated RBD from controls (nigrosome, substantia nigra neuromelanin) as well as RBD subtype (ie, RBD with MCI or cortical thinning); possible prognostic value for DLB (DBM); all markers require independent study confirmation

DAT scans = presence of DA transporters in the basal ganglia

Functional MRI

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Biomarkers for pheno-conversion

Tissue biopsy	Look for phosphorylated alpha-synuclein deposits				
Colon biopsy	Diagnostic	Low	Moderate	24% and 100%[82]	Invasive; poor sensitivity
Major salivary glands	Diagnostic	Low	Moderate	89% and 100%[83]	Invasive, surgeon needed for sampling; high sensitivity if glandular tissue obtained
Minor salivary glands	Diagnostic	Moderate	Moderate	50% and 97%[84]	Invasive, surgeon needed for sampling; poor sensitivity
Skin biopsy	Diagnostic, prognostic, monitoring, combined	Moderate	Moderate	58%–87% and 100%[35,86,87]	Easy to do, minimally invasive, but analysis requires expertise; might help distinguish PD and DLB from MSA[51]
	C7, C8, T10 paraspinal, leg via IMF techniques				
Genetic testing	TBD				
GBA variants	Prognostic	Moderate	Moderate	NA	Might help predict the rate of phenoconversion[95]
SNCA 5′ variants	Prognostic	Moderate	Moderate	NA	Might help predict the rate of phenoconversion[96]

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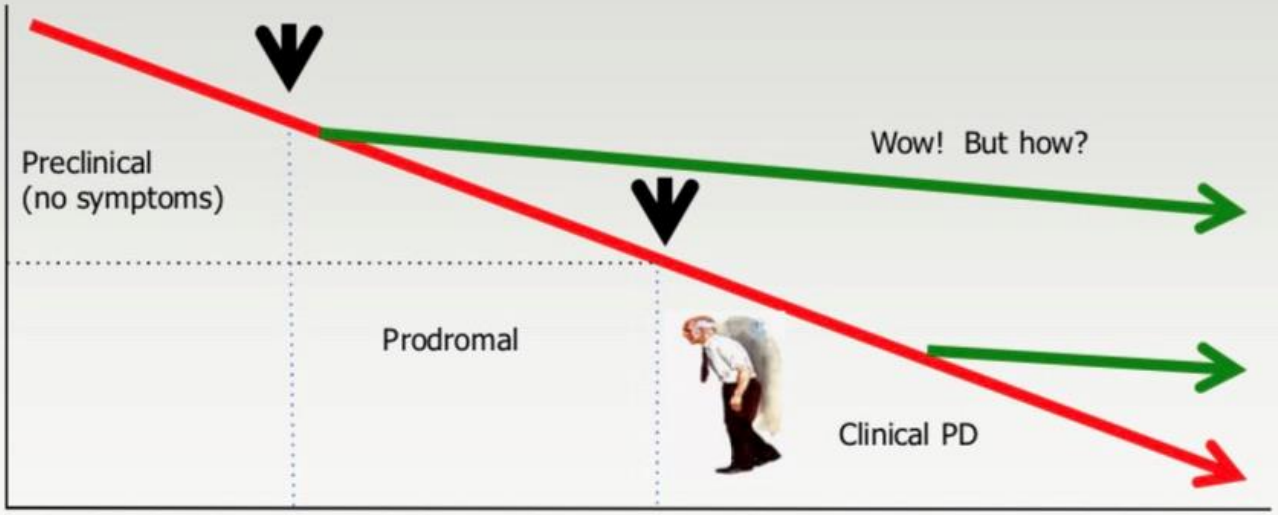
International Parkinson and Movement Disorder Society

Can we do something?



- No better group for Neuroprotection
  - Early (up to 10 years)
  - High risk
  - **Untreated** (extremely important for trials)

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Neuroprotective Trials in REM Sleep Behavior Disorder

The Way Forward Becomes Clearer

Ronald B. Postuma, MD, MSc

Neurology® 2022;99:S19-S25. doi:10.1212/WNL.0000000000200235

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- **As neuroprotective therapies are being developed, interest is turning to prodromal stages to test and eventually use these therapies, while there is still time to prevent irreversible degeneration.**
  - **Any neuroprotective therapy against a progressive neurodegenerative disease should be applied as early as possible in the disease course.**

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- In most series, the interval between development/ diagnosis of RBD and defined NDD averages 10–15 years.
  - olfaction (20 years)
  - autonomic dysfunction (10–25 years)
  - motor and cognitive abnormalities have prodromal intervals of 5–8 years.
    - progress slowly initially, followed more rapid loss soon before phenoconversion, so testing only has sufficient specificity in the 2–3 years before diagnosis

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Neuroprotective Trials in REM Sleep Behavior Disorder

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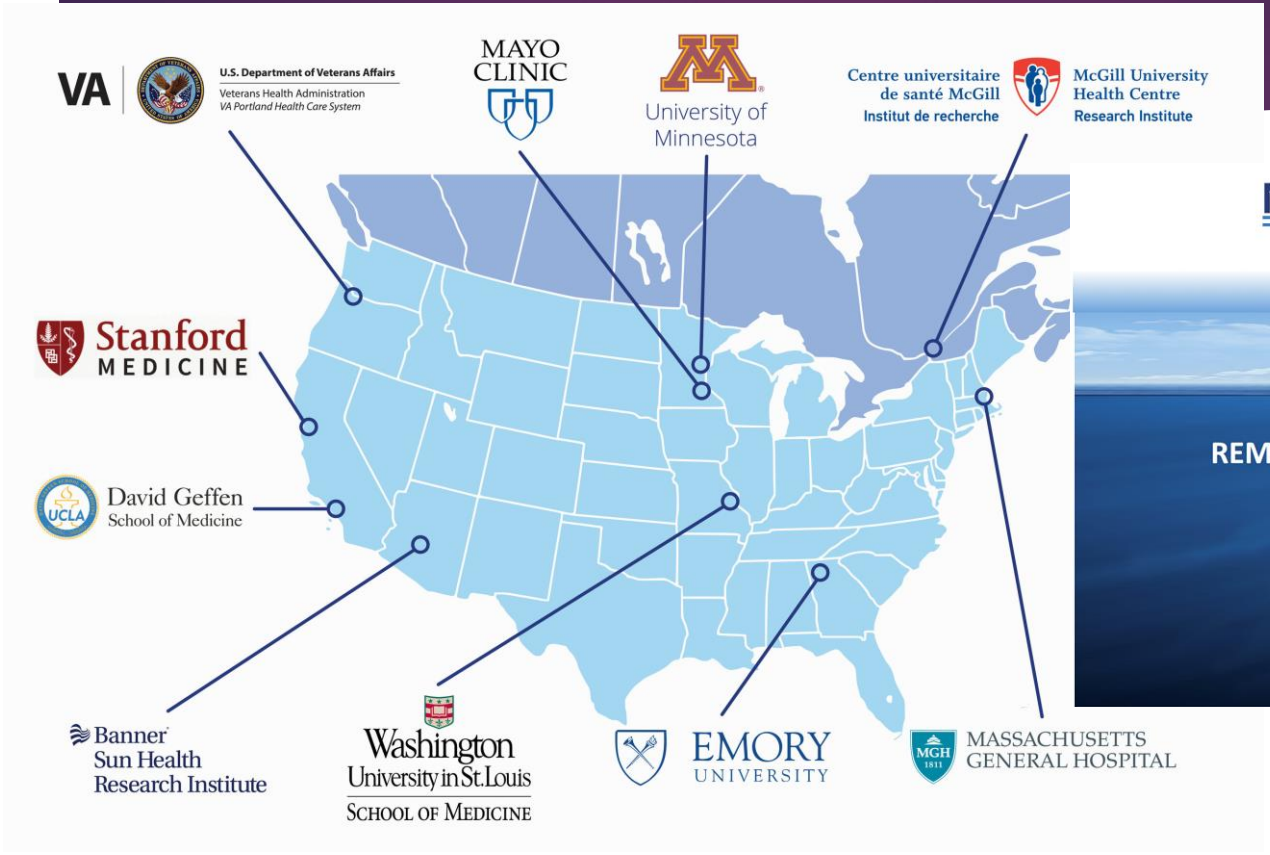
- **Targeted therapies**
  - **Synuclein**
    - **Passive immunotherapy, active immunization, small molecule aggregation inhibitors, and antisense therapy to reduce synuclein synthesis**
  - **Lysosome and Glucocerebrosidase A**

***no clinical trials yet, but likely coming**

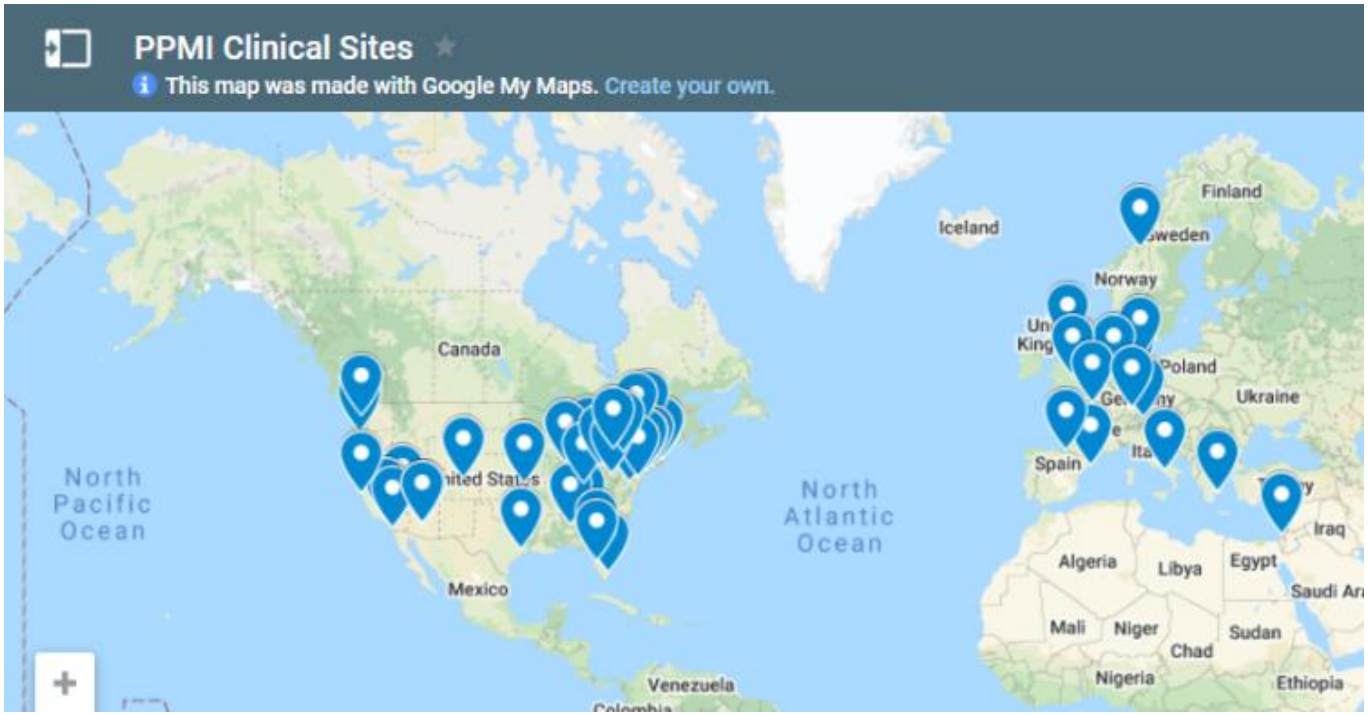
NAPS CONSORTIUM

For REM Sleep Behavior Disorder



Clinicaltrials.gov NCT03623672

Parkinson's Progression Markers Initiative



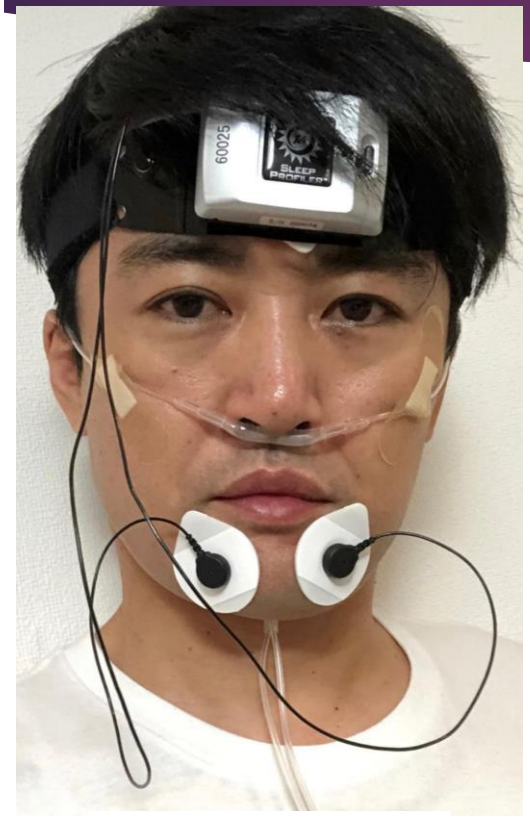
Pilot Study Comparing Home Sleep Profiler to In-laboratory Polysomnogram for RBD Diagnosis

Banner Sun Health Research Institute

NIH National Institutes of Health

- Gregory Lazarz, MD, Joyce Lee-Iannotti, MD, Dan Levendowski, Cyrus Guevarra, RPSGT, Jason Jones, RPSGT, David Shprecher, DO MSci
- Objective: To compare the Sleep Profiler (SP), an FDA-approved device for home evaluation of sleep disorders, to the gold standard sleep laboratory polysomnogram (PSG) in evaluation of dream enactment behavior.
- Background: Diagnosis of REM sleep behavior disorder (RBD) is strongly associated with developing synucleinopathies, particularly Lewy body dementia and Parkinson disease, but requires PSG for confirmatory diagnosis. Capturing RBD during a one-night PSG can be challenging due to night-to-night variability of dream enactment behaviors and can be costly to repeat.

Our Research

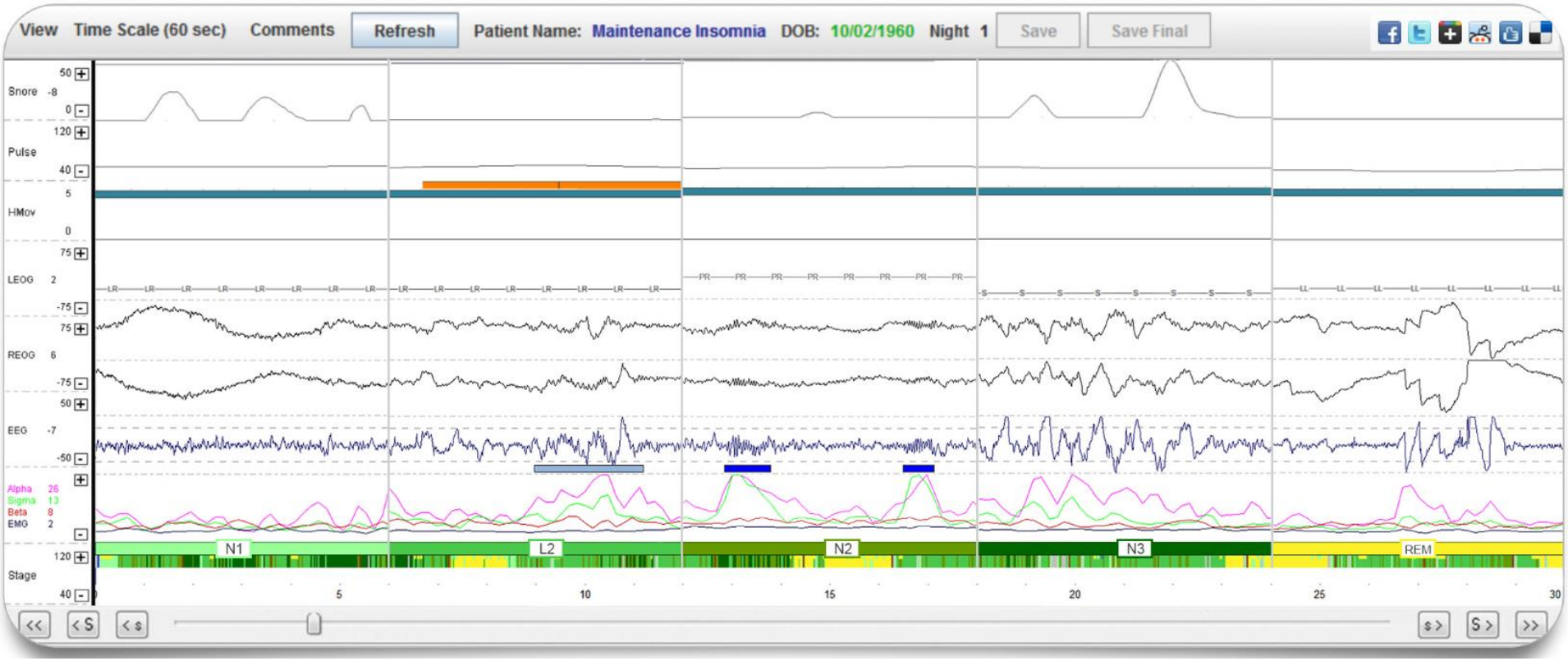


Advanced Brain Monitoring

- **Methods: During an overnight PSG (with seizure and four-limb RBD protocol), we simultaneously collected Sleep Profiler data on 6 subjects recruited with recurrent dream enactment behavior but no evidence of neurodegenerative disease. Independent sleep reviewers analyzed the data from**

3 channels of frontal EEG
Pulse rate and ECG
Quantitative snoring
Head movement and head position
Sub-mental EMG

Sample-Sleep-Profiler-Signals



Our Research

- **Results:**
  - **Sleep efficiencies by PSG and SP were 85.3% and 84.6%, respectively, while the median sleep times were identical (358 min).**
  - **The median sleep onset latency for the PSG was 16 min and 22 min for the SP with a median difference of 5 minutes.**
  - **The PSG and SP REM percentages were 14.5% and 13%, with a median difference of 1.3%.**
  - **4 out of 6 subjects had REM sleep without atonia (RSWA) and concordant dream enactment on both the PSG data and the SP data**
  - **Of the 4 subjects with RSWA, 3 had newly diagnosed obstructive sleep apnea (mean AHI 13.3, range 9.7-16.2/hr).**

Our Research

- **Conclusions: The Sleep Profiler is worthy of larger scale validation studies to show equivalence with PSG in diagnosis of RBD. We suggest the SP be configured to include capabilities to measure airflow signals to screen for sleep apnea and monitor movement in all four limbs for better detection of RSWA. Such studies should also measure potential benefits in terms of cost and feasibility of recruitment of RBD subjects into neurodegenerative disease research trials.**
- **To come…**

RBD Severity Scale - Patient Version (RBDSS - PT)

You are answering this questionnaire because you have been diagnosed with REM sleep behavior disorder (or RBD). Acting out dreams at night is often caused by RBD. Normally when we dream, we are unable to move. However, in RBD, you are capable of moving during dreams. These questions are to help us understand how severe your RBD is.

Because you may not be aware what you do while asleep, we encourage you to answer these questions with the **help of a bed partner** or someone who lives with you, if available.

A. Introductory questions

1. Do you live alone? Yes ☐ No ☐
   If yes, skip to question 3.

   1a. Do you currently have a bed partner (that is, someone who sleeps most nights in the same bed as you)? Yes ☐ No ☐
   If yes, skip to question 2.

   1b. Did you *used* to sleep with a bed partner and had to move apart because of your acting out of dreams? Yes ☐ No ☐

2. Who is providing information for this questionnaire right now?
   - ☐ Myself, with no other assistance
   - ☐ Myself, with the assistance of my bed partner
   - ☐ Myself, with someone who lives with me, but is not my bed partner.

3a) Over the **last month**, how often did you have **disturbing dreams or nightmares**?
   - ☐ Never (**skip** to question 4)
   - ☐ Rarely (<1 time per week),
   - ☐ Occasionally (1-2 times per week),
   - ☐ Frequently (3-7 times per week),
   - ☐ Very frequently (>7 times per week; more than once per night)

3b) Overall, how distressing are these dreams/nightmares to you?
   - ☐ Not at all
   - ☐ Mild - They might be unpleasant, but they do not really bother me much
   - ☐ Moderate - Enough to disturb my sleep or make me anxious about falling asleep
   - ☐ Severe - They are very bothersome, enough to disturb my function during the daytime

4a) Over the **last month**, how often have you **talked loudly or yelled during your sleep**? ('loudly' means enough that you might wake an average person who is in the room with you).
   - ☐ Never (**skip** to question 5)
   - ☐ Rarely (<1 time per week),
   - ☐ Occasionally (1-2 times per week),
   - ☐ Frequently (3-7 times per week),
   - ☐ Very frequently (>7 times per week; more than once per night)

4b) Overall, how distressing have sleep talking/yelling episodes been to you over the last month?
   - ☐ Not at all
   - ☐ Mild - They might be unpleasant, but they do not really bother me much
   - ☐ Moderate - Enough to disturb my sleep or make me anxious about falling asleep
   - ☐ Severe - They are very bothersome, enough to disturb my function during the daytime

5a) Over the **last month**, how often did you **hit, kick, or thrash out** during your sleep?
   - ☐ Never (**skip** to question 6)
   - ☐ Rarely (<1 time per week),
   - ☐ Occasionally (1-2 times per week),
   - ☐ Frequently (3-7 times per week),
   - ☐ Very frequently (>7 times per week; more than once per night)

5b) Overall, how severe are the movements, over the **last month**?
   - ☐ Not at all
   - ☐ Mild - I may be temporarily wakened, but no impact on my sleep overall.
   - ☐ Moderate - Bothersome enough to disturb my own sleep
   - ☐ Severe - Very disruptive to my own sleep. It is severe enough to cause significant impact during the day or is potentially dangerous.

6a) Over the **last month**, how many times did you injure either yourself or your bed partner because of movements during your sleep?
   - ☐ Never
   - ☐ Rarely (Once)
   - ☐ Occasionally (More than once)

6b) Rate the most severe injury over the last **month** to yourself or bed partner related to movements during your sleep
   - ☐ None
   - ☐ Mild - Short duration pain, or a small cut or bruise, but no bothersome pain or impaired function the following day
   - ☐ Moderate - Enough to either cause bothersome pain that persisted into the next day or impair the ability to function well in daily life the next day
   - ☐ Severe - Enough to require medical attention, cause persistent and bothersome pain for more than a week, or impair the ability to function well in daily life for more than one week

N3 Page 1 of 21 Site Initials Date ID Version4_Dec2009 NAPS

Red: Frequency
Blue: severity and distress
Categories: Dream content, Vocalizations, movements, injuries

THE UNIVERSITY OF ARIZONA College of Medicine Phoenix

Continued Validation of the RBD symptom severity scale (RBDSSS) in the North American Prodromal Synucleinopathy (NAPS) consortium

Andrea O. Busicescu, BA, University of Arizona College of Medicine, Phoenix
Parichita Choudhury, MD, Joyce K. Lee-Iannotti, MD, Pooja Rangan, MBBS, MPH, Ron Postuma, MD, on behalf of the NAPS consortium

Banner Health

NAPS CONSORTIUM For REM Sleep Behavior Disorder

Introduction and Research Question

REM Sleep Behavior Disorder (RBD) is a parasomnia characterized by dream enactment. The International RBD Study Group developed the RBD symptom severity scale (RDSSS) to assess symptom severity in clinical and research practice. The objective of this study is to assess the psychometric and clinimetric properties of the RBDSSS in participants enrolled in the North American Prodromal Synucleinopathy (NAPS) Consortium for RBD.

Materials and Methods

NAPS participants with polysomnogram-confirmed RBD and their bedpartners completed the RBDSSS (patient and bed-partner versions). The RBDSSS is an 8-item questionnaire, assessing frequency and severity/impact of dream content, vocalizations, movements, and injuries associated with RBD, with higher scores indicating more severe symptoms. Total scores were derived by multiplying assigned point values for frequency and severity (for each question) and summing them for individual RBDSSS-PT scores (maximum=54) and RBDSSS-BP scores (maximum=38). Item response theory (IRT) with graded response model was used to assess RBDSSS properties and responses to individual questions on the instrument.

Results

Demographic Parameter	Total cross-sectional data (n=261)
Age, mean ± SD	65.3 ± 9.96
Sex, male (%)	210 (80.5%)
Age of symptom onset	51.9 ± 15.7
Education	16.2 ± 3.0
RBD Severity Scale Data	
RBDSSS-PT, median (IQR)	10 (4-18)
RBDSSS-BP, median (IQR)	8 (4-15)
CGI-S, median (IQR)	3 (3-4)
Medication use (Lifetime), n (%)	
Any	207 (80.5%)
Clonazepam	127 (48.7%)
Melatonin	146 (55.9%)
Other (dopamine agonists etc.)	20 (7.7%)
Current medication use, n (%)	
Any	184 (71.0%)
Clonazepam	106 (40.6%)
Melatonin	117 (44.8%)
Other	14 (5.4%)

Table 1: Characteristics of participants and RBD severity scores

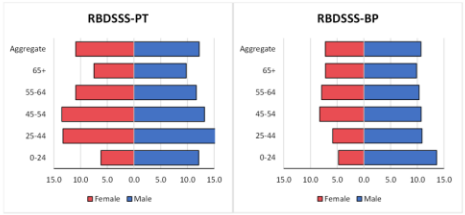


Figure 1: Distribution of RBDSSS-PT (a) and RBDSSS-BP (b) by sex and age of symptom onset. Red bars = women, blue bars = men.

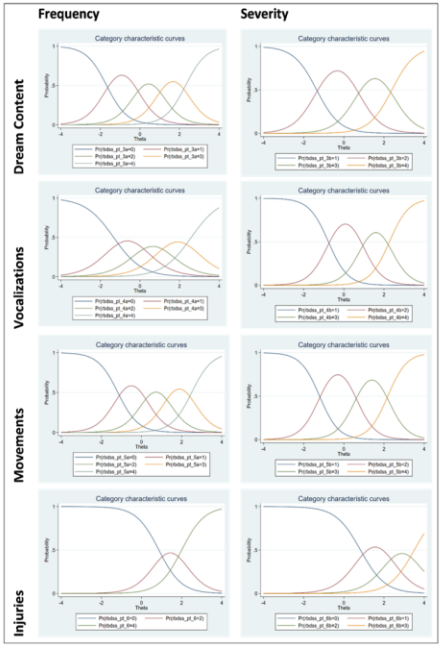


Figure 2: Category characteristic curves for RBDSSS-PT. The left column represents frequency questions and right column represents severity/impact questions. These curves demonstrate the probability of endorsing a category for each item ('never' to 'very frequently' and 'not at all' to 'severe' for impact). Theta on the X-axis demonstrates the RBD severity trait (overall RBD-severity), and each color curve corresponds to a number (denoted in the legend) which is the category in ascending order (0=none, 1=rarely, 2=occasionally, etc.). (IRT data table)

Summary

- The RBDSSS demonstrates good internal consistency, validity, and discriminatory value to measure RBD severity.
- Questions about movement severity were most sensitive in discriminating overall RBD severity, detecting slight variations. Questions about injury severity were most indicative of highest RBD severity.
- Analysis using graded response theory showed that the RBDSSS assesses RBD severity effectively across a range of overall severity, and all items presented high to very-high discriminatory properties. Individual item responses can thus be used as an outcome measure for treatment efficacy.
- Participant-reported RBD severity was no different between sexes, but RBD severity reported by bed-partners and clinicians was lower for female participants. Women were also less likely to be treated with medications.
- Future direction: Longitudinal assessment to define minimum clinically meaningful change. Correlation of scale scores with measured symptoms via home monitoring devices.

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“Better than a thousand days of diligent study is one day with a great mentor.”

-Japanese Proverb

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World Parkinson's Day
11 April 2021
www.parkinsonsnsw.org.au

April is National Parkinson's Awareness Month

https://www.parkinson.org/parkinsons-awareness-month

Parkinson's Foundation

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Jeffrey Charles Reese
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Thank you!

Questions?

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