Treatment of Parasomnia in Old Age

-REM sleep behavior disorder를 중심으로

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- Epidemiology
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- Biomarkers of conversion to α-synucleinopathy
- Management

Introduction

- Normal sleep structure
  - Cycles of rapid eye movement (REM) sleep and non-REM sleep
  - REM sleep
    - Generalized muscle atonia, REMs, activated EEG, dreaming
  - NREM sleep
    - No muscle atonia, absent or diminished dreaming
- REM sleep behavioral disorder (RBD)
  - Abnormal behaviors
    - Usually dream enactment
  - Excess of muscle tone (REM sleep without atonia, RSWA) and/or phasic muscle twitching during REM sleep

Introduction

- Idiopathic RBD (iRBD) vs. symptomatic (or 2ndary RBD)
  - 2ndary RBD is mainly associated with α-synucleinopathy neurodegenerative diseases (PD, DLB, MSA), narcolepsy type I and antidepressants
- Dream enactment: usually start >2hr after sleep onset
  - Predominantly in the 2nd part of the night (longest REM sleep episode)
- Most motor events are simple elementary movements even in severe RBD patients
- Violent behaviors are rarely observed
  - If present, occurs frequently during phasic REM sleep epochs

Epidemiology

- Limited data on the prevalence of iRBD d/t requirement of video PSG (vPSG)
- Koreans study (>60 years of age) Kang, S. et al., *Sleep*, 2013
  - Initial vPSG to identify abnormal muscle tone → telephoned to screen for dream-enactment behavior
  - 1.15% for PSG-demonstrated iRBD
  - 5% for asymptomatic RSWA
- HypnoLaus study – population-based Haba-Rubio, J. et al., *Sleep*, 2017
  - 1.06%
- Spain study (>60 years of age) – primary care centers Pujol, M. et al., *Sleep Med*, 2017
  - 0.74%

Epidemiology

- 2ndary RBD
  - 30-50% of PD have RBD
  - >70% of DLB or MSA have RBD
  - 50% of narcolepsy have RBD or RSWA
- Risk factors
  - Strongest risk factors: increased age, male sex
  - iRBD
    - fifth or sixth decade of life
    - Pesticide exposure (and farming), head injury
    - Smoking (iRBD > w/o RBD)
    - Lower level of education
    - Higher prevalence of ischemic heart disease, COPD and depression
  - 2ndary RBD
    - Starts at younger age (Narcolepsy type I, autoimmune or brain disorder)

Epidemiology

- RBD is by far the strongest prodromal marker of α-synucleinopathy
- Risk of α-synucleinopathy
  - 38% of RBD developed PD or dementia at a mean interval of ~4 years after diagnosis → 81% after ~14years
  - Neurodegeneration or MCI after 5 years → 91% after >14years

Pathophysiology

- Sublaterodorsal tegmental nucleus (SLD)
  - Rats with REM sleep hypersomnia
    - SLD has a role in the generation of muscle atonia in REM sleep
    - SLD neurons express vesicular glutamate transporter 2 (vGLUT2)
      - Transport glu into synaptic vesicles
      - Required for glu neurotransmission
      - Selectively active during REM sleep
      - Inactivation of vGLUT2 induces RSWA and RBD and 30% decrease in REM sleep quantities
  - RBD patients
    - Reduced signal intensity in the LC and SLD → suggesting RBD is induced by neurodegeneration of SLD glutaminergic neurons
    - However, RBD patients do not have decreased REM sleep quantitiy ➔ another system downstream of the SLD neuron is involved

Pathophysiology

- GABA and glycine-containing n. of the ventral medulla
  - Projection from SLD neurons
  - Projects to spinal motor neurons
    - Hyperpolarization of motor neurons during REM sleep → muscle atonia
  - Cat study
    - Lesions of the ventral medulla induce RSWA
  - Rat study
    - Genetic inactiviation with vesicular inhibitory amino acid transporter (vGAT) in ventral medulla → RSWA and RBD
  - RBD patients
    - Inflammatory regions of the ventral medulla
    - Post-mortem study: Lewy bodies and neuronal loss in the ventral medulla

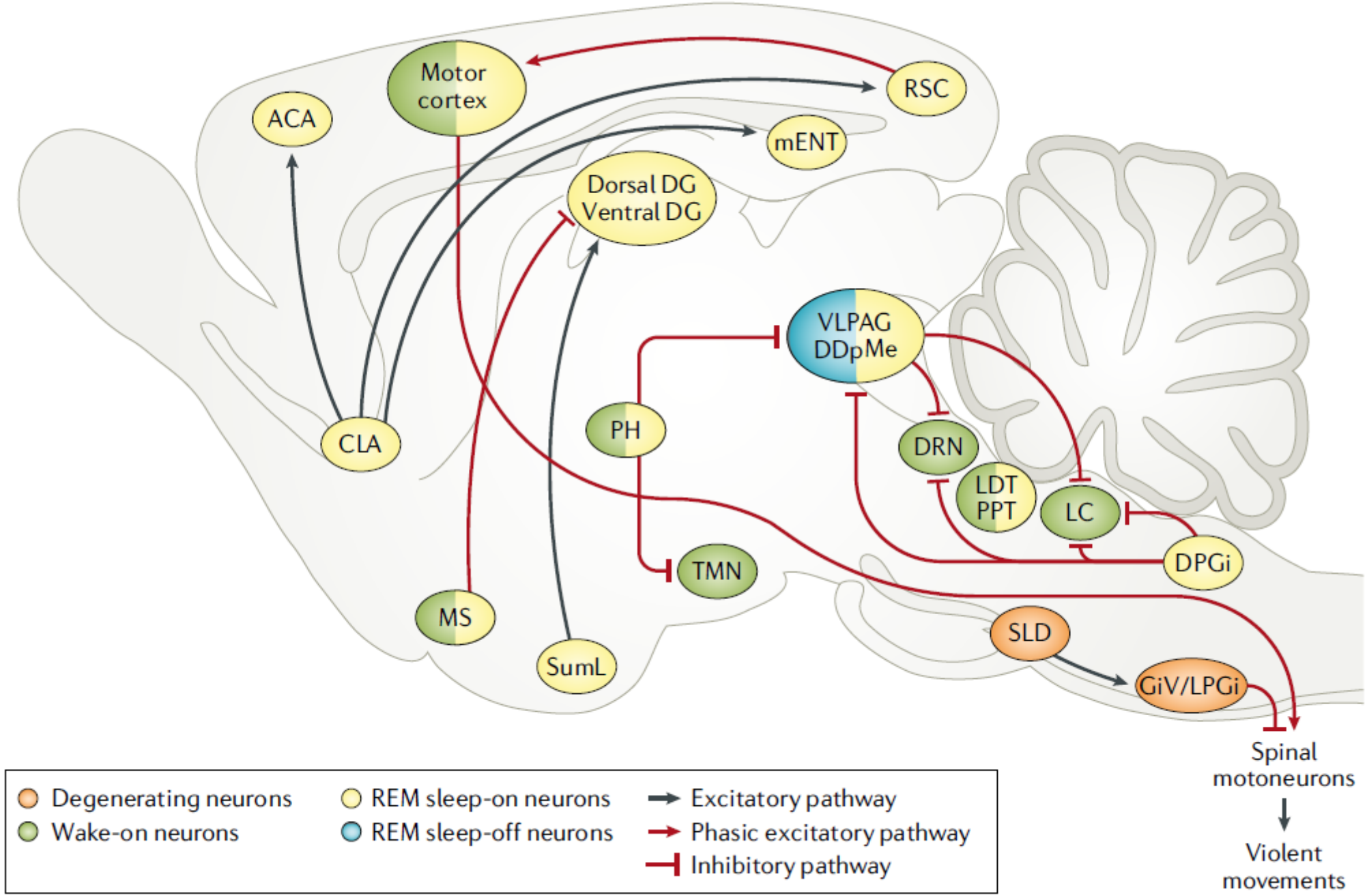


Fig. 2 | **Neuronal network generating REM sleep and inducing REM sleep without atonia and RBD.** In rats and mice,

Diagnosis & Screening

- International Classification of Sleep Disorders, Third Edition (ICSD-3)
- Dream enactment behavior
  - Excessive body and limb jerking
  - Complex, goal-directed behavior
    - Gesturing, punching, kicking, sitting up, leaping from bed
  - A large spectrum of non-violent behaviors

Box 2 | **ICSD-3 diagnostic criteria for RBD**

To obtain a diagnosis of rapid eye movement (REM) sleep behaviour disorder (RBD), the following criteria must all be met.

- Repeated episodes of sleep-related vocalization and/or complex motor behaviours.
- These behaviours are documented by polysomnography to occur during REM sleep or, based on a clinical history of dream enactment, are presumed to occur during REM sleep.
- Polysomnography demonstrates REM sleep without atonia.
- The disturbance is not better explained by another sleep disorder, mental disorder, medication or substance abuse.

ICSD-3, International Classification of Sleep Disorders, Third Edition.

Table 1. Findings of reported dream content and witnessed abnormal behaviors in RBD patients

	IRBD (n=102)	MSA (n=67)	IPD (n=65)	DLB (n=17)
Self-awareness of behaviors (%)	53.9	23.9	35.4	29.4
Unpleasant dream recall (%)	92.1	65.7	86.2	82.4
Most frequent unpleasant dreams				
Attacked by someone (%)	84.3	38.8	67.7	64.7
Arguing with someone (%)	58.8	35.8	53.1	41.2
Chased by someone (%)	52.9	35.8	53.8	47.1
Falling from a cliff (%)	48.0	29.9	44.6	11.8
Attacked by animal (%)	42.2	26.9	32.3	29.4
Most frequent abnormal behaviors				
Talking (%)	96.1	89.6	95.4	94.1
Shouting (%)	89.2	79.1	89.2	82.4
Swearing (%)	33.3	26.9	29.2	23.5
Crying (%)	42.2	52.2	49.2	41.2
Laughing (%)	54.9	61.2	47.7	52.9
Singing (%)	17.6	13.4	13.8	0
Punching (%)	83.3	73.1	69.2	64.7
Kicking (%)	78.4	56.7	66.2	41.2
Falling out of bed (%)	77.5	46.3	38.5	82.4
Patients injured (%)	55.9	13.4	15.4	41.2
Bed partners injured (%)	23.5	6.0	10.8	5.9

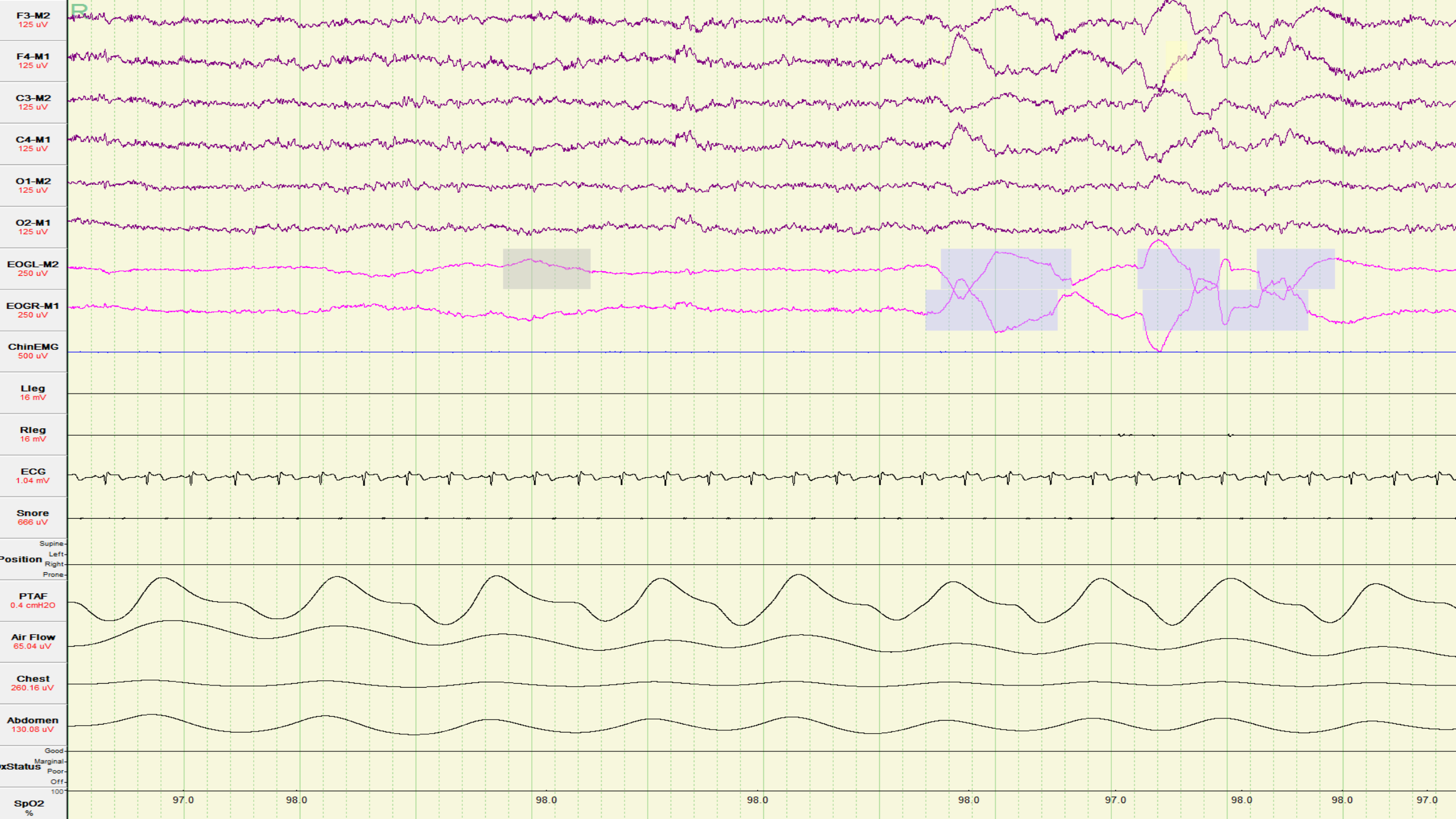
Adopted from Iranzo et al, Sleep Medicine Reviews 2009

Diagnosis & Screening

- Eliciting a clear history of dream enactment behavior is difficult
  - Half of patients are not aware of the behaviors, and remember the associated dream content
  - Information from bedpartners is important
- A typical history of dream enactment behavior → Probable RBD diagnosis
- vPSG → Definitive diagnosis

REM sleep without atonia

- Definition
  - Excessive sustained muscle activity (SMA, tonic) in chin EMG
  - Excessive transient muscle activity (TMA, phasic) in chin/limb
  - Any chin EMG
- Rule: one or more of the followings
  - SMA in chin EMG (recommended)
  - TMA in chin or limb EMG (recommended)
  - Any chin or limb EMG in 50% or more of 10 mini-epochs (acceptable)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O1-M2
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ChinEMG
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Rleg
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ECG
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Snore
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Position
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PTAF
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Air Flow
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Chest
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Abdomen
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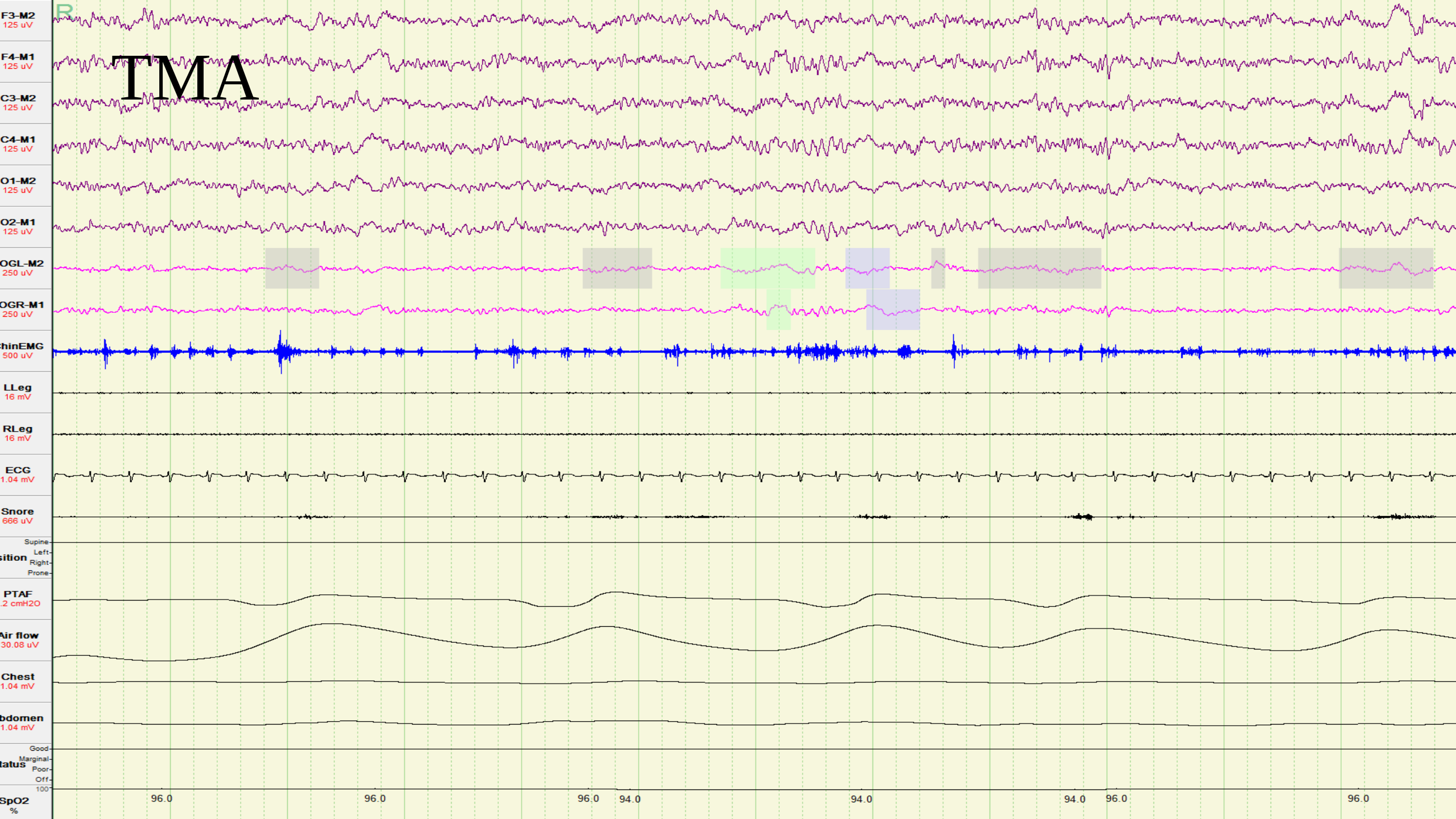
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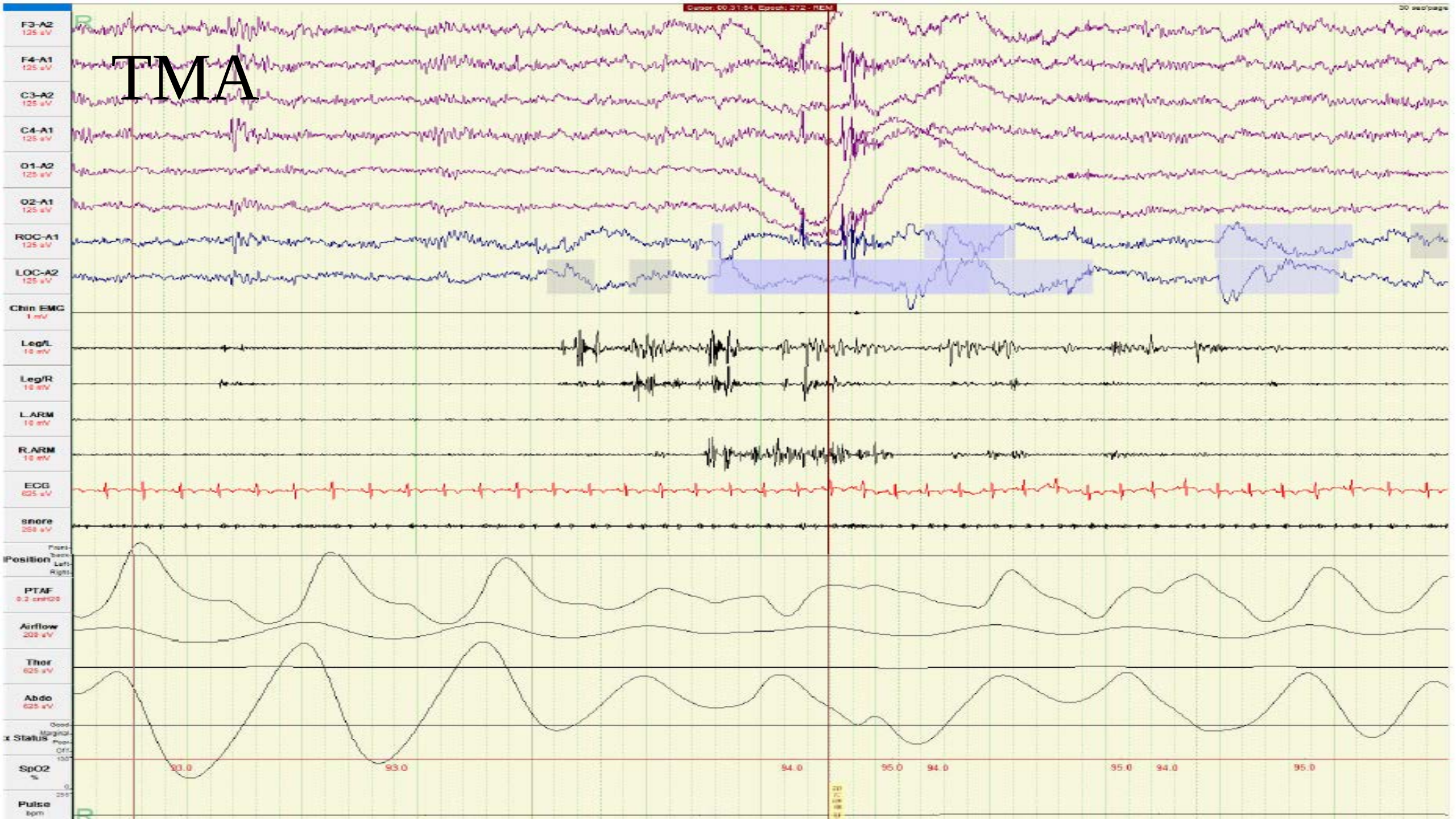
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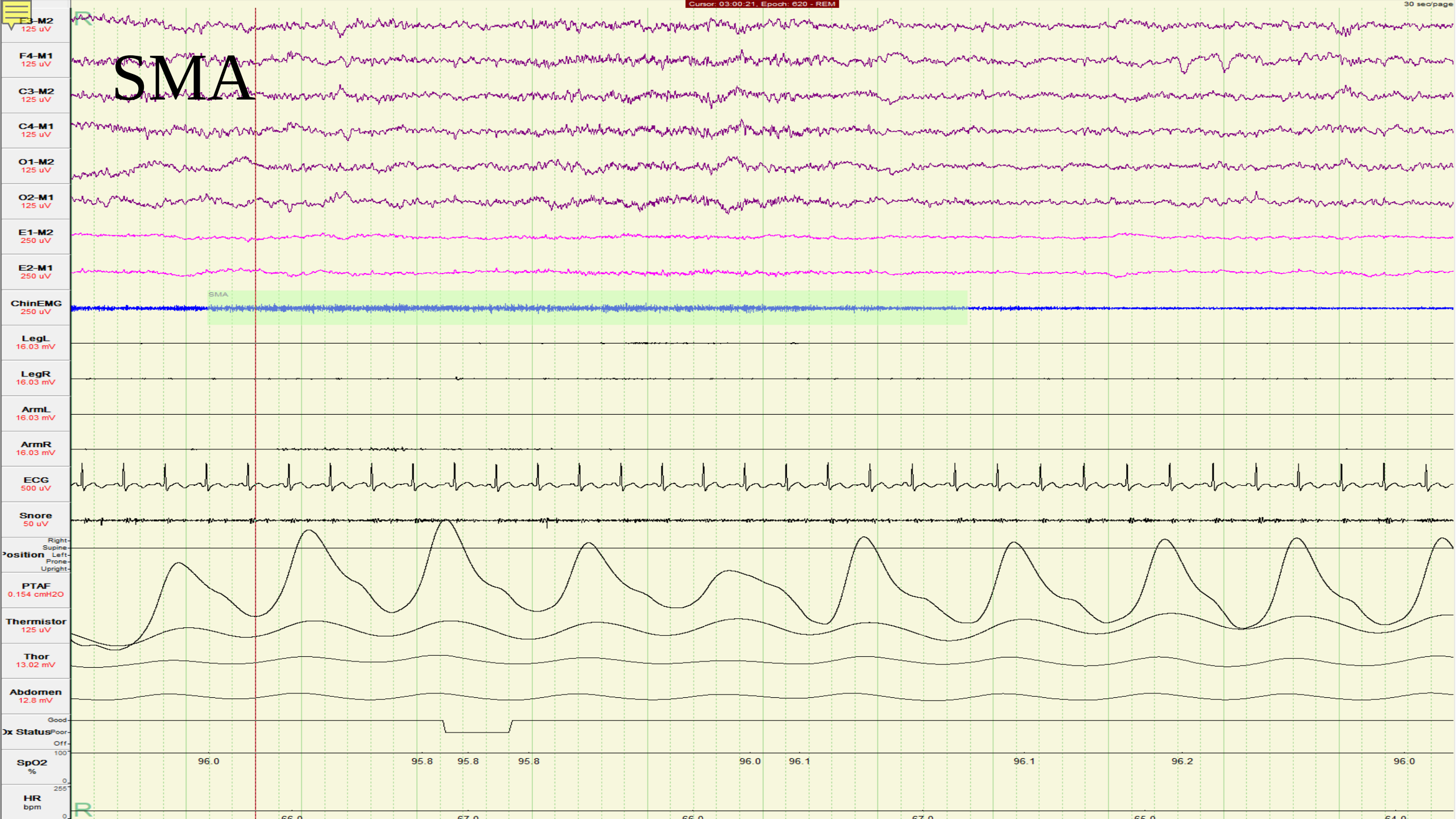
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ECG
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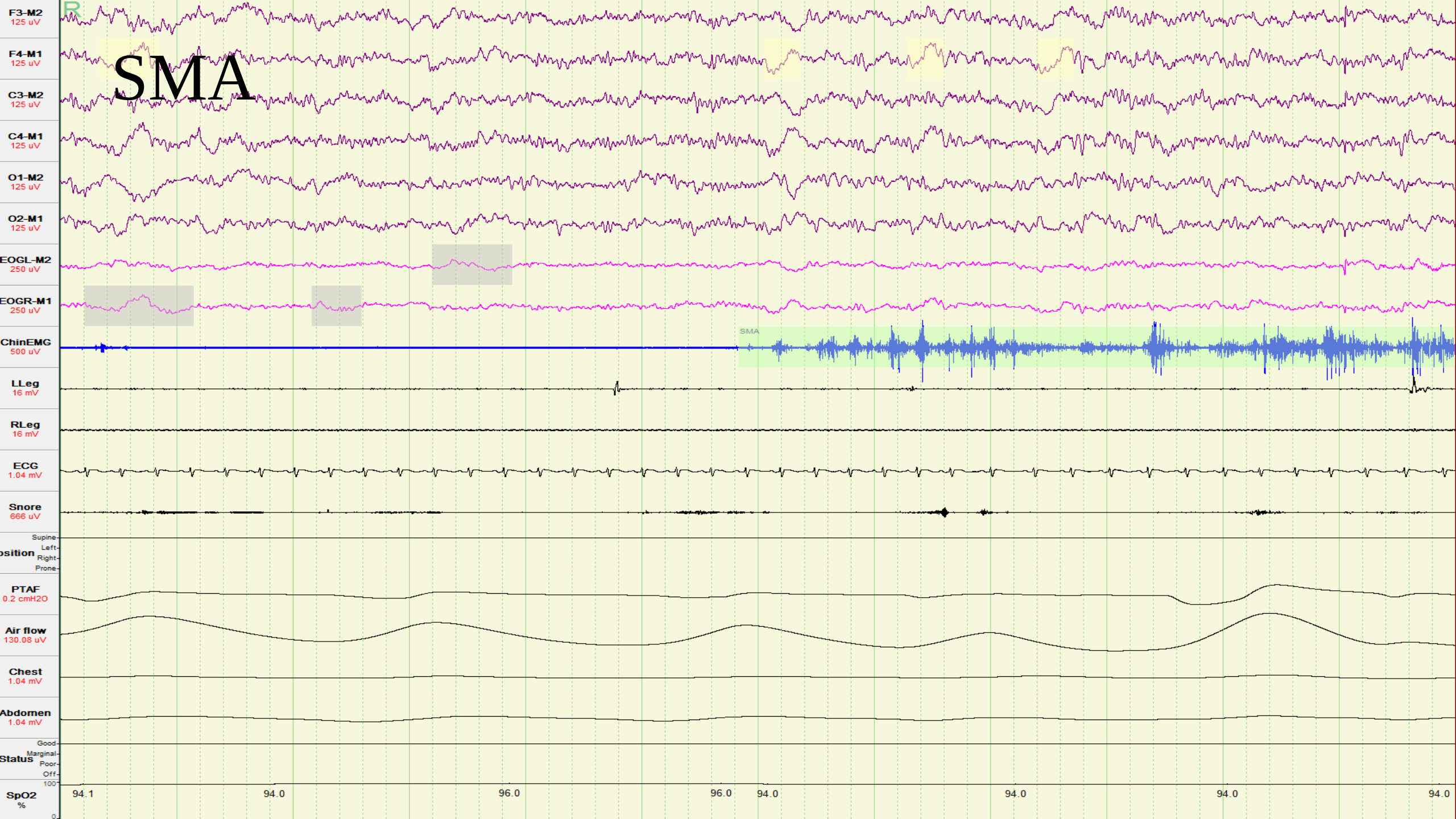
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ECG
1.04 mV
Snore
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Position
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Air flow
130.08 uV
Chest
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Abdomen
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Status
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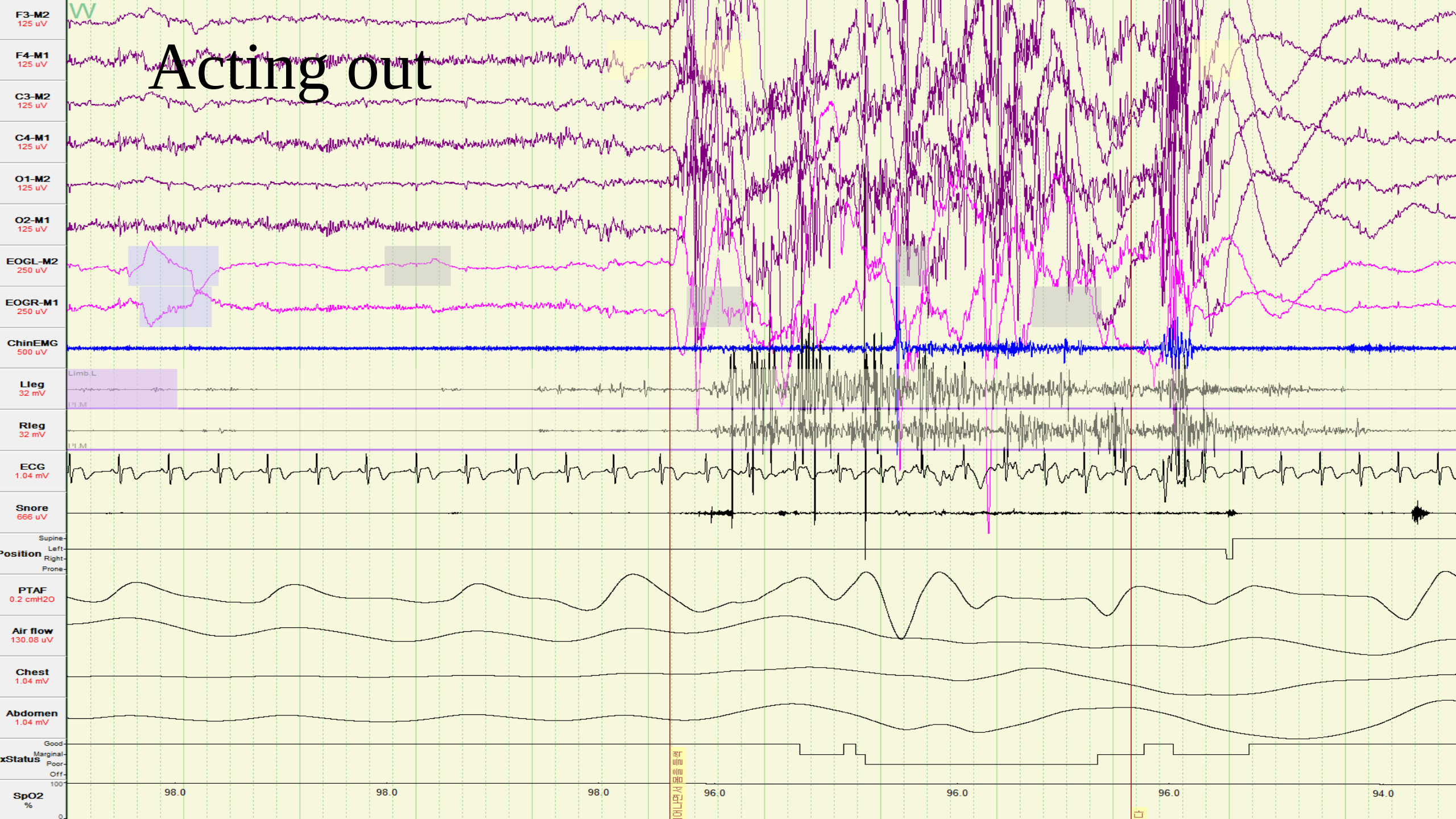
Dream enactment

Dream enactment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ChinEMG
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ORIGINAL ARTICLE

Automated Assessment of Quantitative REM Sleep without Atonia for Diagnosis of REM Sleep Behavior Disorder

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Objective: This study was performed to determine the diagnostic cutoff value of quantified tonic and phasic rapid eye movement (REM) sleep without atonia (RSWA) automatically calculated from chin and limb muscle electromyograms (EMG) for diagnosis of REM sleep behavior disorder (RBD). **Methods:** Nocturnal video polysomnographic data of 57 patients diagnosed with RBD and 29 age- and sex-matched controls were reviewed. Tonic activity was measured using submentalis EMG, and phasic activity was measured using submentalis and bilateral anterior tibialis EMG. The proportion of epochs with tonic and phasic activity during the entire REM sleep period was quantified using a self-developed automated algorithm. **Results:** The RBD group showed significantly more tonic activity compared with the control group (28.87±36.92% vs. 12.94±31.69%, respectively, p<0.001). The diagnostic cutoff value of quantified submentalis tonic RSWA for RBD showing the best optimal sensitivity and specificity was 0.99% [sensitivity, 77.2%; specificity, 79.3%, area under the receiver operating characteristic curve (AUC), 0.76]. Cutoffs of phasic RSWA were 47.53% when assessed in the submentalis only (sensitivity, 1.8%; specificity, 100%; AUC, 0.46), 0.10% in the anterior tibialis (sensitivity, 66.7%; specificity, 55.2%; AUC, 0.55), and 0.10% in both the submentalis and anterior tibialis (sensitivity, 70.2%; specificity, 51.7%; AUC, 0.53). **Conclusion:** This study provided evidence for the diagnosis of RBD using an automated method by assessing RSWA. Tonic activity in the submentalis muscle showed better sensitivity and specificity for diagnosis of RBD than did phasic activity.

Key Words: REM sleep behavior disorder; REM sleep without atonia; Automated algorithm

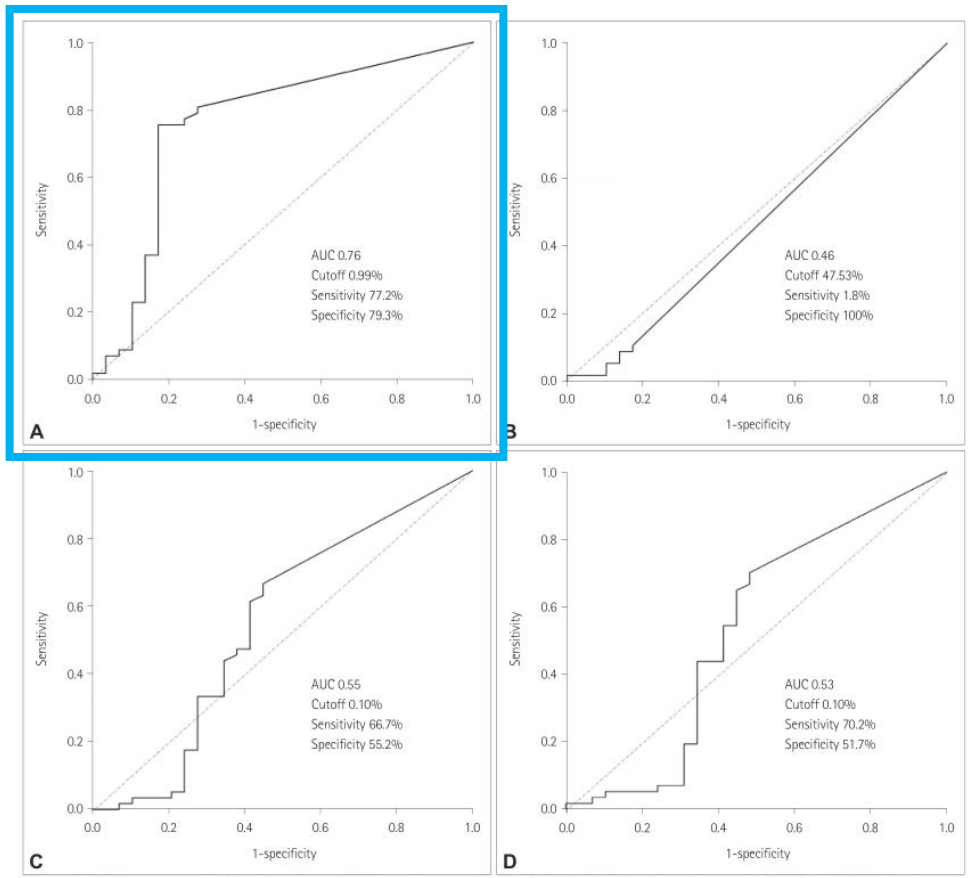

Figure 1. ROC curves evaluating the ability of RSWA to diagnose RBD. (A) Tonic RSWA in the submentalis. (B) Phasic RSWA in the submentalis. (C) Phasic RSWA in the anterior tibialis. (D) Phasic RSWA in both the submentalis and anterior tibialis. ROC: receiver operating characteristic, AUC: area under the ROC curve, RSWA: rapid eye movement sleep without atonia, RBD: rapid eye movement sleep behavior disorder.

Diagnosis & Screening

- RSWA w/o any history or vPSG-recorded behavioral manifestation
  - Frequent among elderly and PD patients
  - Might represent an early stage of RBD
  - A risk factor for neurodegenerative disease
  - 10/14 individuals were positive for at least one biomarker for neurodegeneration after 8.6yrs
- Screening tools
  - The RBD Screening Questionnaire (RBDSQ): 13 items
    - Sensitivity (91%), specificity (77%)
  - Hong Kong Questionnaire (RBD-HK): 12 items
    - Sensitivity (82%), specificity (87%)
  - Innsbruck RBD inventory: 5 items
    - High sensitivity (91%), specificity (86%)

Biomarkers

- UPDRS score of >3 at any time point: 4-fold increased risk
- MCI increased risk for dementia-first DLB conversions.

	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]
Motor function					
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					
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

Miglis et al., *The Lancet Neurology*, 2021

Biomarkers

- Olfactory loss: 2-3 fold increased risk
- Impaired color vision: 3 fold increased risk

	Subtype	Availability	Cost	Sensitivity and specificity	Remarks
Olfaction					
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					
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
Autonomic function					
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					
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

Miglis et al., *The Lancet Neurology,* 2021

Biomarkers

	Subtype	Availability	Cost	Sensitivity and specificity	Remarks
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
Tissue biopsy					
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]
Genetic testing					
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]

RSWA=rapid eye movement sleep without atonia, SINBAR=Sleep Innsbruck Barcelona group, AUC=area under the curve, PD=Parkinson's disease, DLB=dementia with Lewy

Miglis et al., *The Lancet Neurology,* 2021

Association of heart rate variability with REM sleep without atonia in idiopathic REM sleep behavior disorder

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Study Objectives: Idiopathic rapid eye movement sleep behavior disorder (iRBD), characterized by rapid eye movement sleep without atonia (RSWA) and dream-enactment behavior, has been suggested to be a predictor of α-synucleinopathies. Autonomic instability, represented by heart rate variability, is a common characteristic of both iRBD and α-synucleinopathies. Previous studies reported that RSWA was associated with autonomic dysfunction and was a possible predictor of phenoconversion. Therefore, we sought to compare heart rate variability between iRBD and control groups and explore the relationship between heart rate variability and RSWA in patients with iRBD.

Methods: Nocturnal polysomnographic data on 47 patients (28 men, 19 women) diagnosed with iRBD based on video-polysomnography and 26 age-matched and sex-matched controls were reviewed. The first 5-minute epoch with a stable electrocardiogram lead II on video-polysomnography was selected from stage N2, wake, and rapid eye movement. For quantification of RSWA, tonic activity was analyzed from the submentalis electromyogram and phasic activity from the submentalis and bilateral anterior tibialis electromyogram channels.

Results: Compared to the control group, the iRBD group showed significant reductions in the standard deviation of the R-R intervals, the root mean square of successive R-R interval differences, and high-frequency values. Quantified tonic activity was inversely correlated with normalized low-frequency values and low-frequency/high-frequency ratios and positively correlated with normalized high-frequency values.

Conclusions: This study implied decreased cardiac autonomic function in patients with iRBD, which showed parasympathetic predominance. Heart rate variability of the patients with iRBD in this study was associated with quantified tonic RSWA, which was previously reported to be a possible predictor of phenoconversion.

Keywords: REM sleep behavior disorder, heart rate variability, autonomic nervous system

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RBD and psychiatric symptoms

- Anxiety, apathy and depression were associated with RBD. Molano J et al., *The Neurology,* 2008
- RBD patients presented higher alexithymia scores. Godin I et al., *Sleep,* 2013
  - Emotional dysregulation may contribute to depression
  - Higher alexithymia score was associated with more nightmare distress
- 44.7% of RBD patients suffered from depressed mood. Hyeong Gon, L. et al, *Psychiatry investigation,* 2016
  - Depression was associated with reduced ability to recall enacted dreams.
  - Depressed RBD patients may have more neurodegenerative changes than non-depressed patients.
    - Neurodegeneration → less attention & more memory impairment → less likely to recall enacted dreams

Management

- The primary goals of Management
  - Minimize dream enactment behaviors, associated w/ injuries and unpleasant dreams
  - To improve patient's and bed partner’s QoL
- Non-pharmacological therapies
  - Comorbid OSA should be treated w/ CPAP to improve RBD-like symptoms
  - Education and counselling
    - Minimize the injury
      - Remove sharp and rigid objects away from the bed
      - Place soft items btw patients and structures
      - To avoid falling from bed, mattress and bedside rails are useful
    - Alcohol can trigger or aggravate RBD

Management

- Pharmacological therapies
  - First, aggravators should be discontinued
    - SSRIs, SNRIs, TCA can aggravate RBD symptoms
    - RBD w/ depression: bupropion can be considered
  - Clonazepam
    - 0.25mg~2mg
    - Most effective: behavior and nightmare
    - Discontinuation of CNZP can result in rebound RBD
    - Drug of choice in individuals w/o substantial cognitive impairment, gait impairment or untreated OSA
    - One study suggests that CNZP reduces tonic activity and decrease number of stage shifts in REM sleep → restore REM sleep modulation

Management

- Pharmacological therapies
  - Melatonin
    - Can be increased to max dose of 12mg/night
      - Melatonin PR: 2~6mg
    - Few adverse effects – headache and somnolence
    - Potentiates the action of GABA on $GABA_A$ Rc on spinal motor neurons → reduction in muscle atonia in RBD
    - Decreases calmodulin affecting cytoskeletal structure and nicotinic acetylcholine Rc in skeletal muscle cells
  - In some patients, combination therapy of clonazepam and melatonin is more effective than using either drug alone.

Management

- Pharmacological therapies
  - No consensus of optimal third-line therapies is available → Trial and error approach should be used
  - Other drugs reported to improve RBD in case reports or small series
    - Ramelteon
    - DA agonists
    - Choline esterase inhibitors – rivastigmine, donepezil
    - Anticonvulsants
    - Antipsychotics – clozapine, quetiapine
    - Levodopa
    - Sodium oxybate
  - DLB with severe RBD and V/H refractory to CNZP and melatonin → quetiapine or clozapine might be reasonable choices.

Management

- Prevention and consultation of conversion to α-synucleinopathy
  - No protective therapies for PD or DLB
  - iRBD can be major target for neuroprotective therapies
- Advise patients
  - To follow a healthy lifestyle
  - To take part in prospective cohort studies

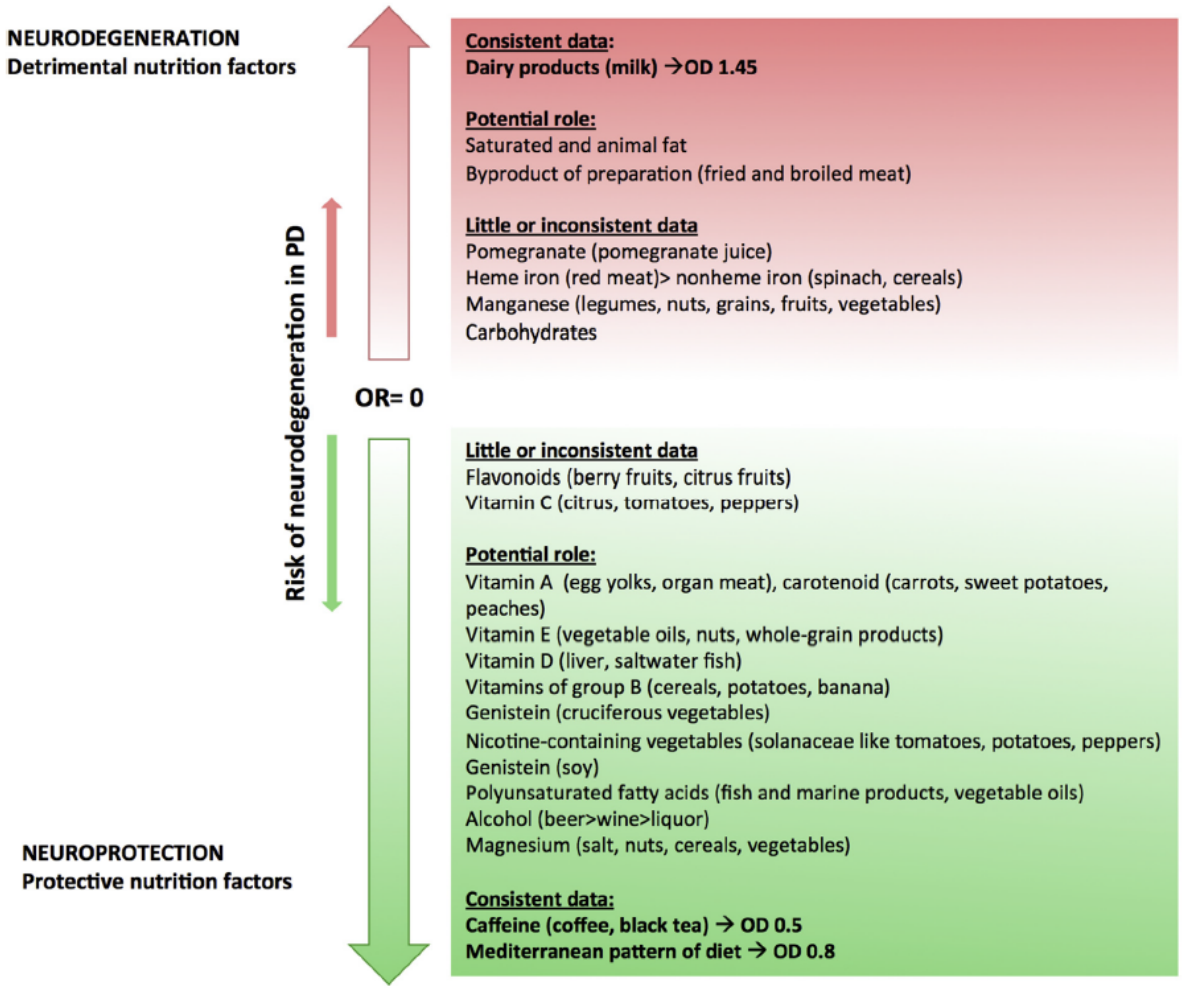

Fig. 4. Dietary risk factors for PD, including eating habits and lifestyle having been associated with higher (red) or lower (green) risk of neurodegeneration in case-conti prospective studies. PD : Parkinson's disease; OD and OR: odd ratio.

Arnaldi et al., *Sleep medicine reviews,* 2017

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