REM without atonia as a marker of neurodegeneration in REM sleep behavior disorder

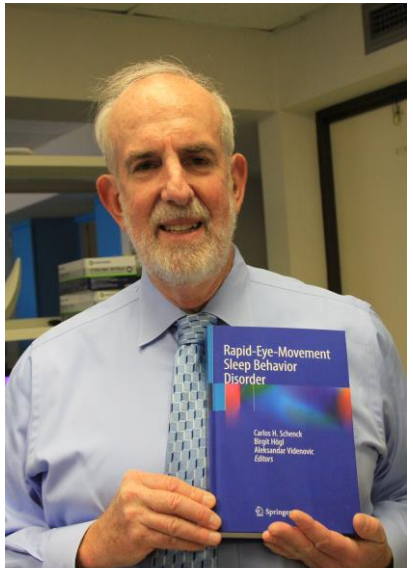
한국노년신경정신약물학회

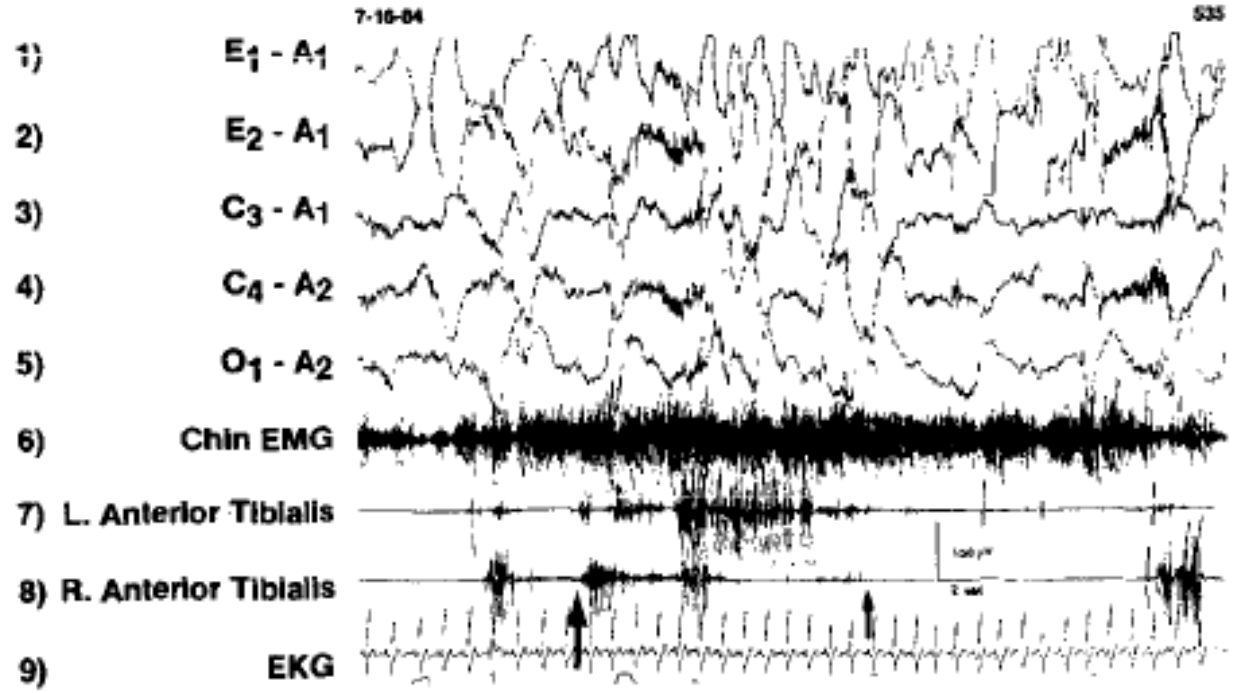
2022-12-09

강동경희대병원 변정익

REM sleep Behavior Disorder

- **Carlos Schenck**
- **1982 University of Minnesota**
- **Mark Mahowald (Neurologist), Andrea Patterson (Tech)**
- **67/M football player, jump out of bed while dreaming**





PSG in Patient 3 (Schenck *et al.*, 1986)
running activity, waving the right arm, vocalizing loudly and strangely

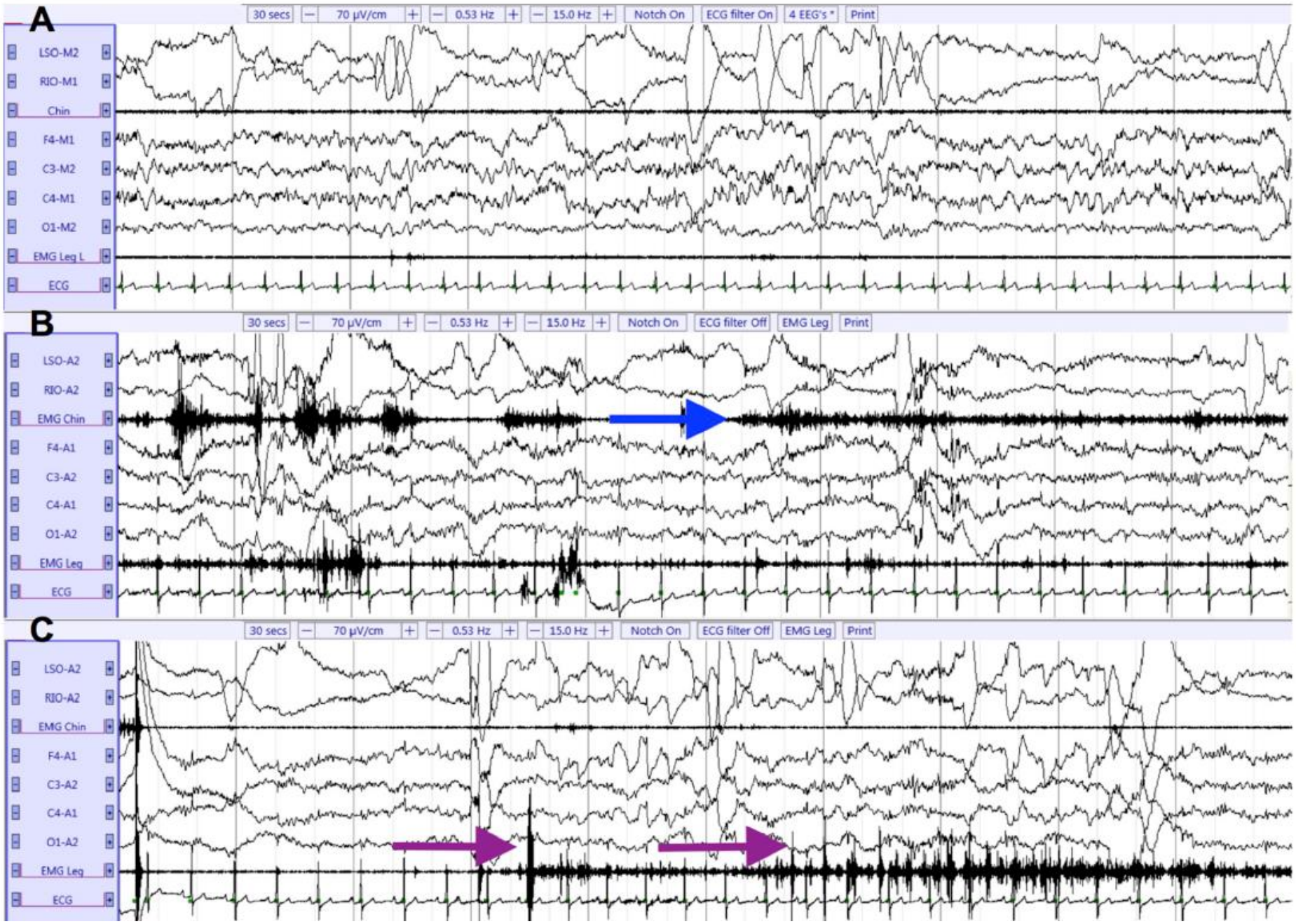
REM sleep Behavior Disorder (ICSD-3)

- Repeated episodes of **sleep-related vocalization and/or complex motor behavior**
- 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**
- **Polysomnographic recording demonstrates REM sleep without atonia (RWA)**
- The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.

➔ **Dream enactment behavior + REM sleep without atonia**

REM without Atonia

- A: normal REM sleep
- B: tonic chin EMG activity
- C: Tonic and phasic chin EMG activity



Scoring REM Without Atonia (RWA) Version 2.6

➔ **Excessive sustained muscle activity (tonic activity) in chin EMG**

- **at least 50% of epoch have chin EMG amplitude at least 2 times greater** than the stage R atonia level (or lowest amplitude in NREM)
- **multiple segment (each duration>5sec) may contribute** to the total duration.

➔ **Excessive transient muscle activity (phasic activity) in chin or limb EMG**

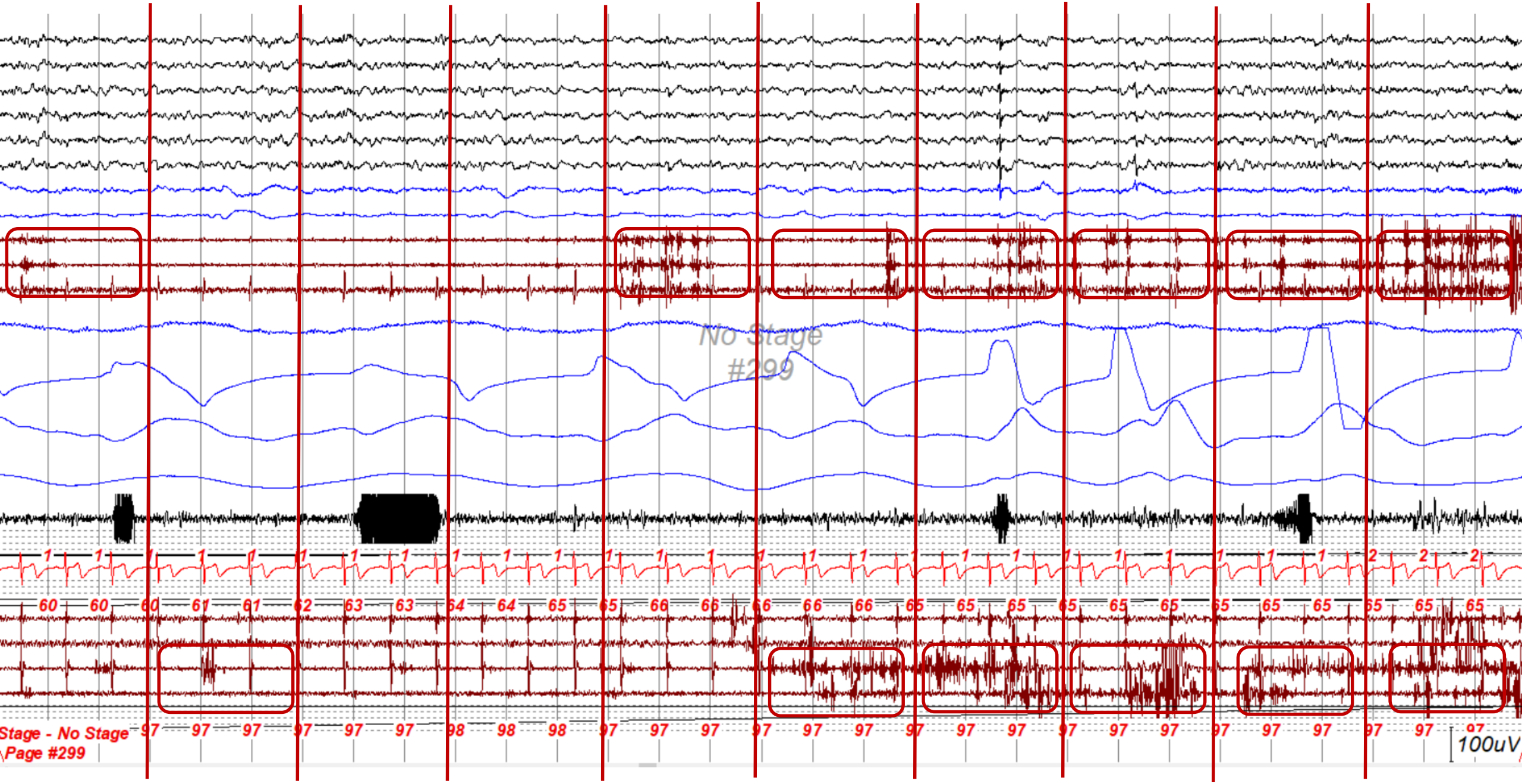
- **3-second mini-epoch**
- **5 of the mini-epochs contain bursts of transient muscle activity** (0.1-5 seconds, EMG amplitude at least 2 times greater) in the chin or limb EMG

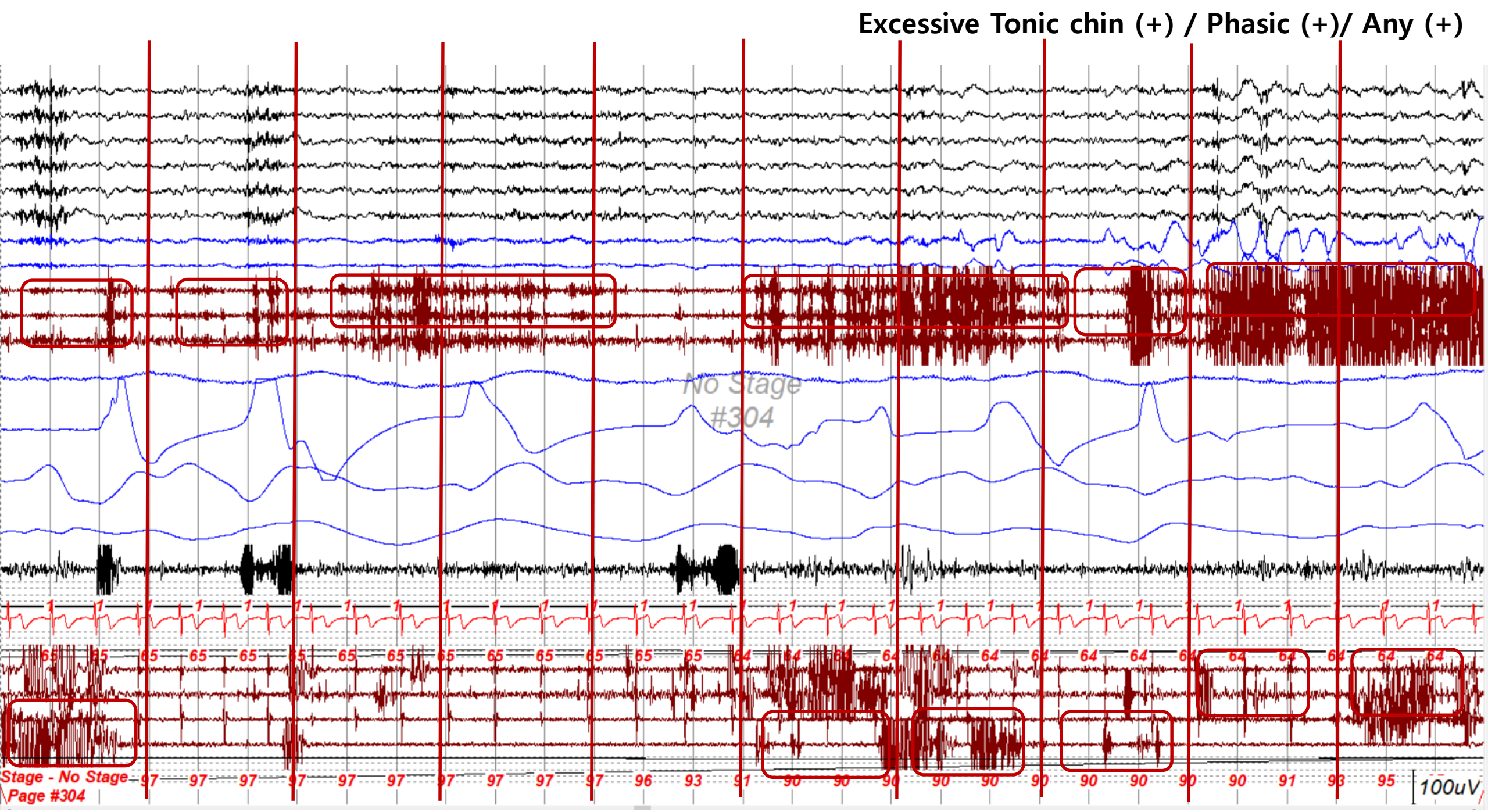
• **Any chin EMG activity**

- chin EMG amplitude at least 2 times greater than the stage R atonia level (or lowest amplitude in NREM)
- without regard to the duration (including bursts of 5 to 15 seconds)

➔ **At least 50% of 3 second mini-epoch contain any chin or limb EMG activity**

Excessive Tonic chin (-) / Phasic (+)/ Any (+)




Excessive Tonic chin (+) / Phasic (+)/ Any (+)
No Stage
#304
Stage - No Stage
Page #304
100uV

Authors	Year	Type	Muscle	Duration	Amplitude	Method	Cut-off
AASM manual	**2020**	Tonic	Submentalis	≥15	>x2 of lowest NREM EMG	manual	-
		Phasic	Submentalis, limbs	0.1~5	>x2 of background EMG		
		Any		≥0.1	>x2 of background EMG		
Montplaisir (Canada)	**1992 2010**	Tonic	submentalis	≥10	>x2 of background EMG	manual	15.0%
		Phasic		0.1~5	>x4 of background EMG		30.0%
Frauscher (SINBAR)	**2012 2014**	Tonic	Submentalis	≥15	>x2 of background EMG	Manual automatic	8.7%
		Phasic	**Submentalis, limb** (TA, **FDS)**	0.1~5			49.7%
		Any		≥0.1			27.2%
McCarter	**2014 2017**	Tonic	**Submentalis**	≥15	>x2 of background EMG	Manual automatic	
		Phasic	**Submentalis, Limb (TA)**	0.1~15	>x4 of background EMG		
		Any		≥0.1			43.4%
Ferry (Italy)	**2010**	RAI	Submentalis	1	>2uV	Automatic	0.8

Comparison of rapid eye movement without atonia quantification methods to diagnose rapid eye movement sleep behavior disorder: a systematic review

Jung-Ick Byun[1], Tae-Won Yang[2,3,4], Jun-Sang Sunwoo[5,], Won Chul Shin[1], Oh-Young Kwon[2,4,6,*,†] and Ki-Young Jung[7,*,†,]

SLEEP 2022

- The diagnostic performance of the manual and automatic approaches for RWA quantification has not been systematically analyzed.
- We performed a systematic review to investigate RWA quantification methods for the diagnosis of RBD.
- **The aim of our study was to compare the diagnostic performance of various RWA quantification methods, including manual procedures and an automated RAI.**

Methods

- The protocol of this study was specified in advance and was registered in PROSPERO (No. CRD42021276445).
- **Inclusion criteria:** studies that provided information for true and false positive (TP and FP) and true and false negative (TN and FN) values by evaluating the performance of manual or automated RWA quantification methods for RBD diagnosis.
- Based on the TP, TN, FP, and FN values, we calculated the **pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the curve (AUC)** using random effects models (using the DerSimonian–Laird method) **by using Meta-DiSc 1.4.**
- A summary receiver operator curve (SROC) was constructed with the Moses-Shapiro-Littenberg method.
- Heterogeneity among studies was evaluated by means of Cochrane Q statistics and the Higgins I^2 index.
- Meta-regression analysis was performed to identify the source of variability by the following predefined influencing factors: age, proportion of males, RBD type (isolated, secondary or unspecified), proportion of REM sleep, and exclusion or arousal or respiratory events.

Results

- Finally, a total of 14 studies met the study criteria and were included in the meta-analysis
- **Manual RWA quantification** was performed in eleven studies.

- Any chin+phasic FDS (3 studies, n=87, cut-off 32%)

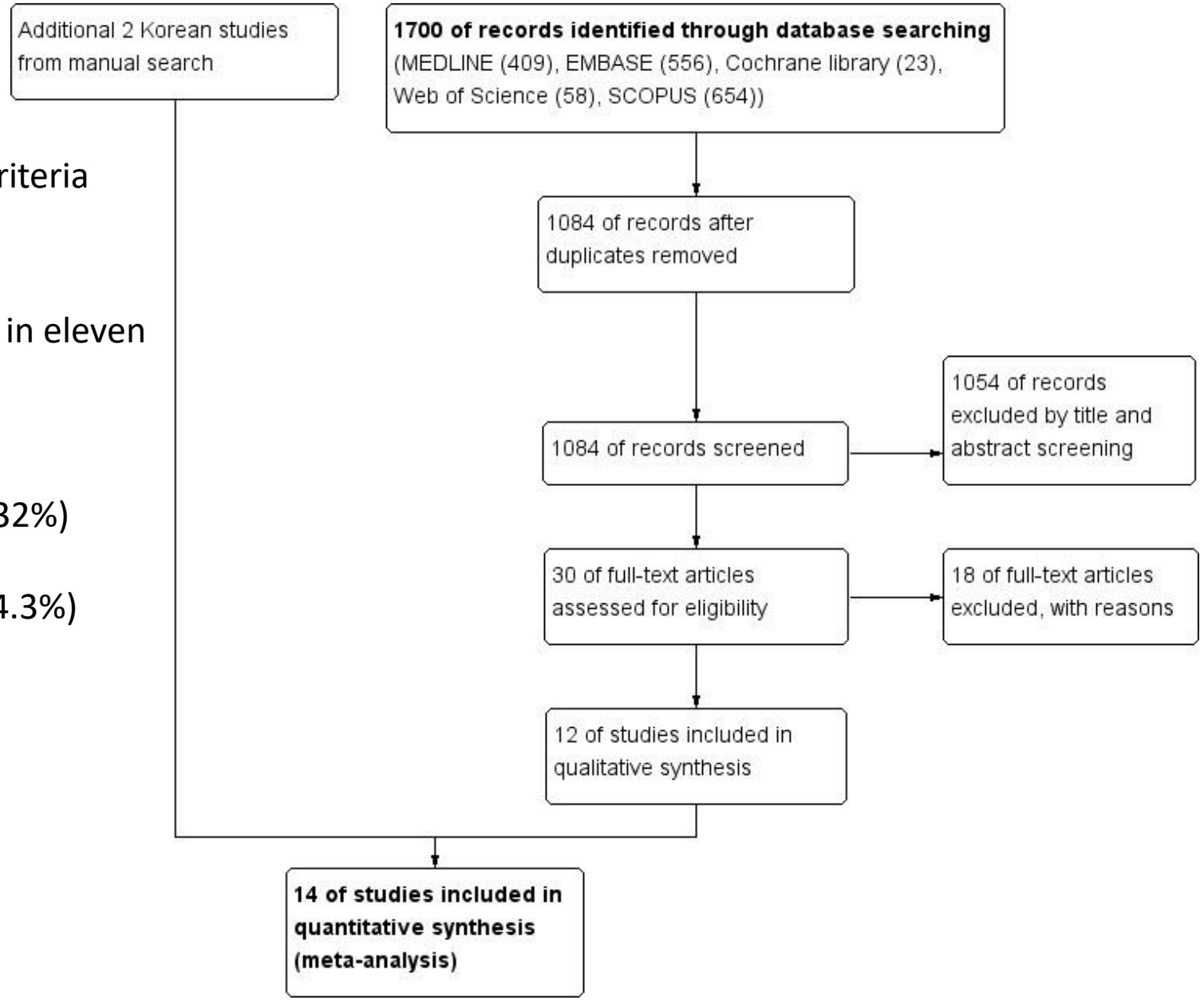
- Any chin+phasic TA (4 studies, n=79, cut-off 34.3%)

- Any chin (6 studies, n=162, cut-off 16.9%)

- phasic chin (11 studies, n=340, cut-off 14.8%)

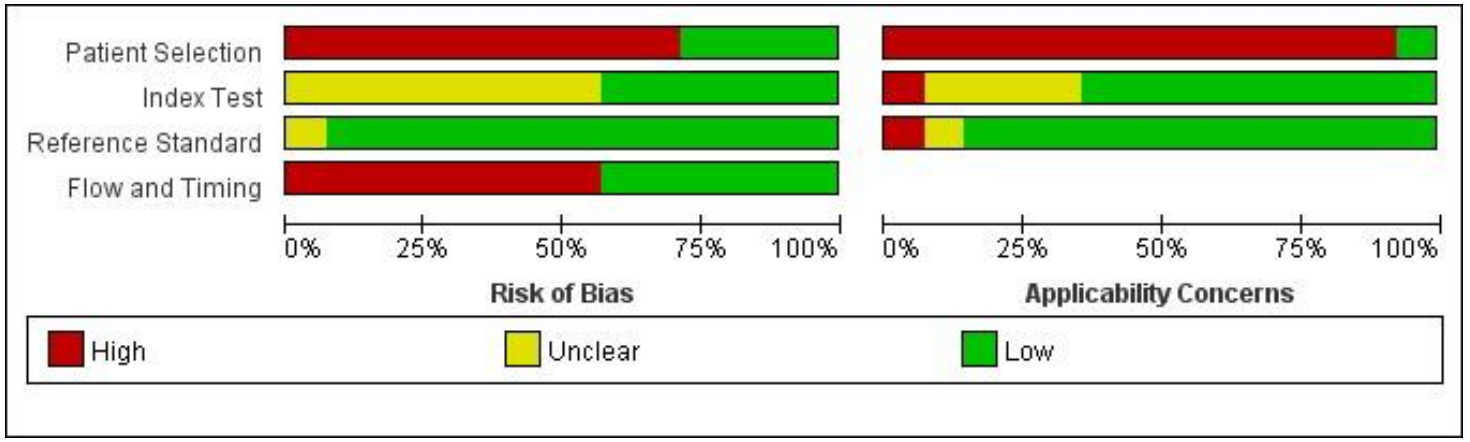
- tonic chin (9 studies, n=305, cut-off 7.9%)

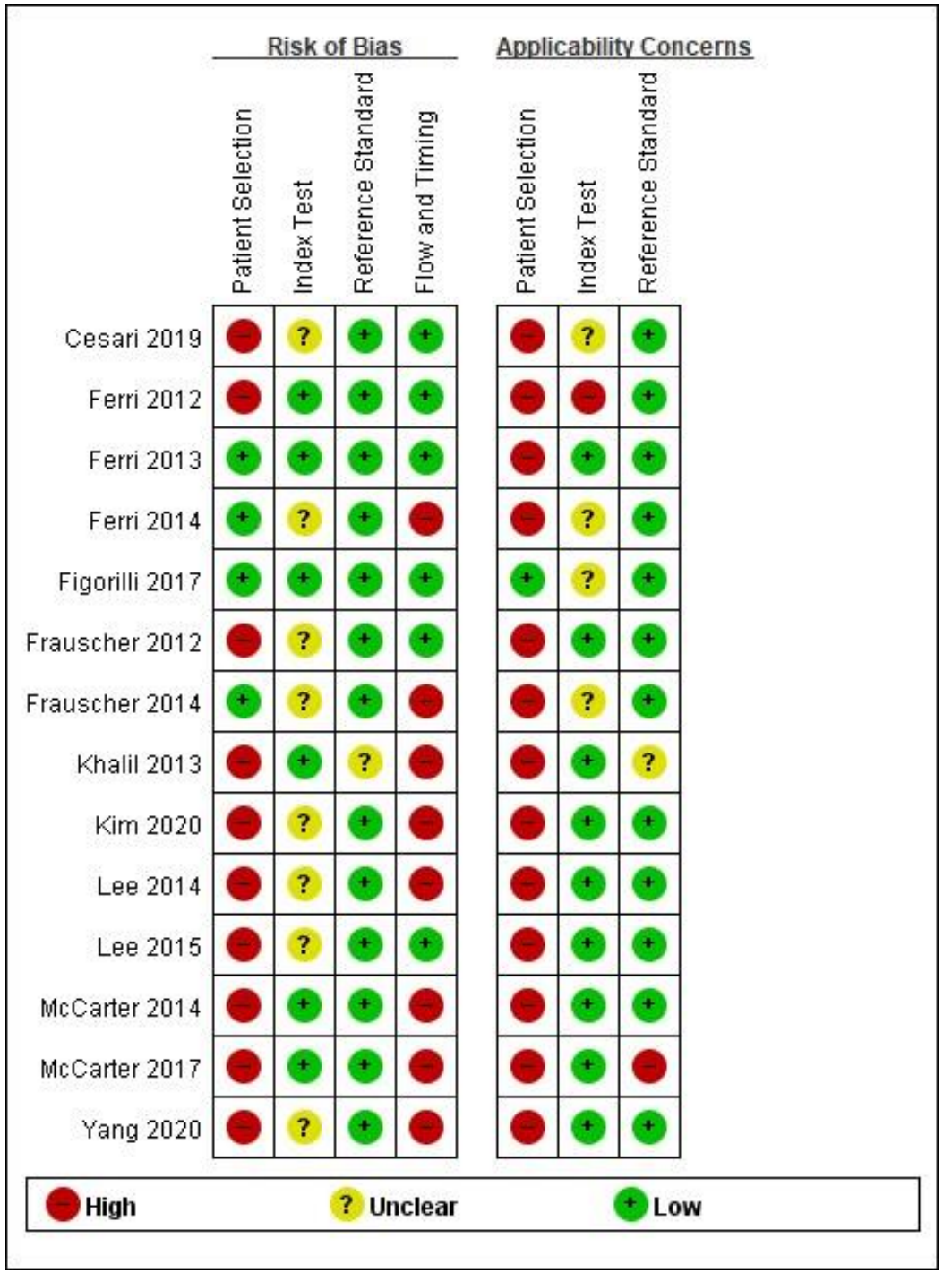
- **RAI** (8 studies, n=248, cut-off 0.87)

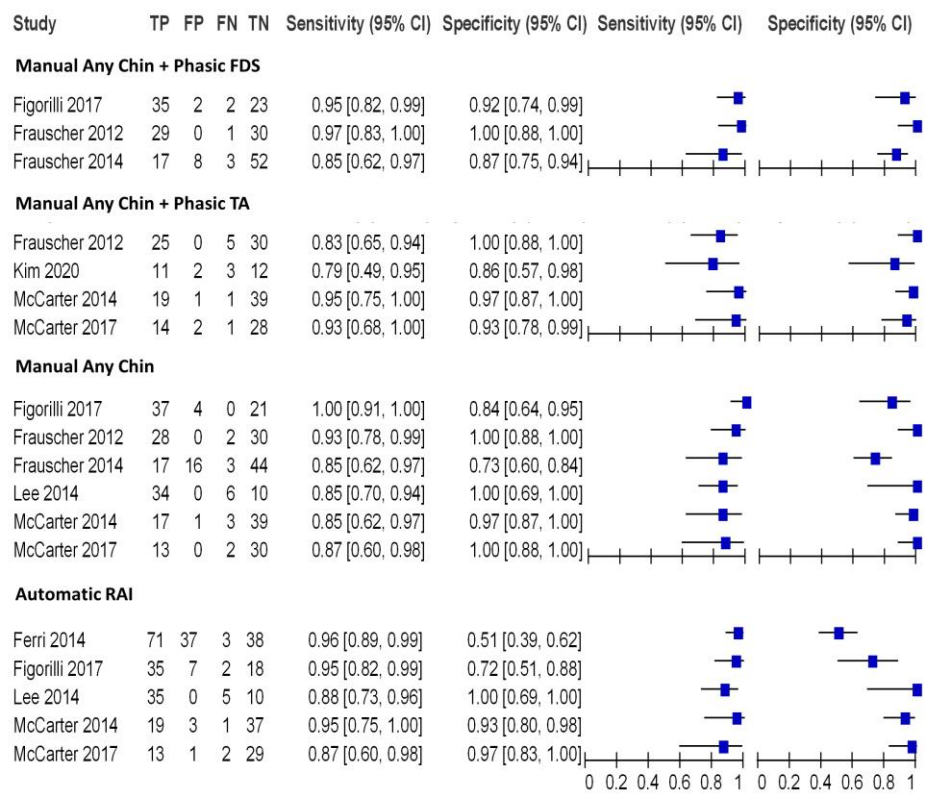


Results: Literature quality

- **Patient selection:** case–control design or had disease controls not healthy controls.
- **Index test:** did not prespecify a cutoff threshold
- **Reference standard:** ICSD criteria to diagnose RBD, and that one was rated ‘low’
- **Flow and timing:** ‘high risk’ because they did not specify RBD duration







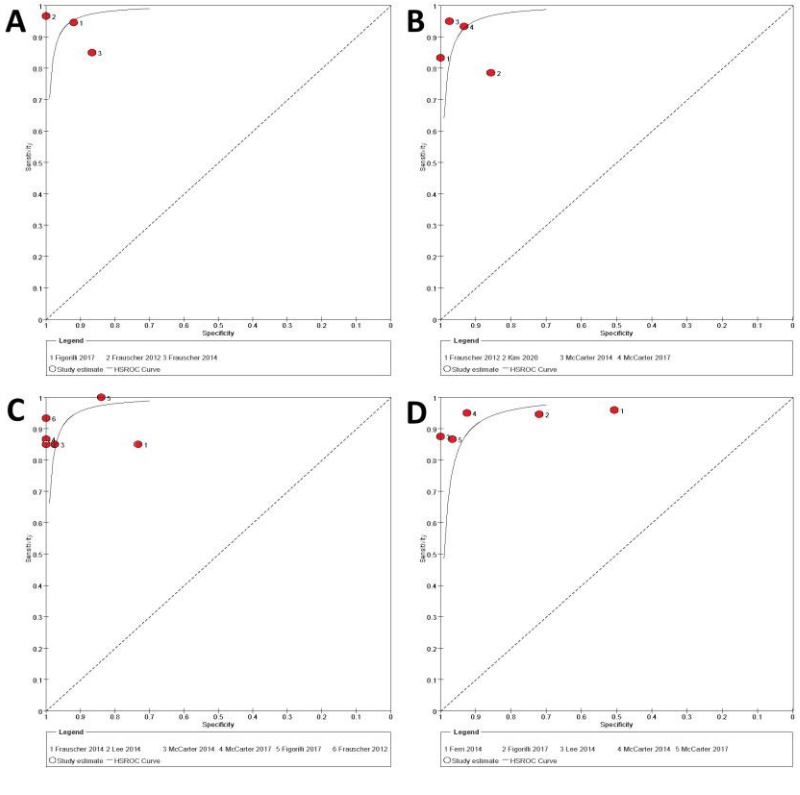


Table 3. Pooled estimates from the current meta-analysis according to the RWA quantification methods for diagnosing REM sleep behavior disorder

Index test	Number of studies	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Diagnostic OR (95% CI)	AUC
Manual (any chin) + phasic FDS	3	0.931 (0.856–0.974)	0.913 (0.846–0.958)	138.80 (21.849–881.72)	0.9686
Manual (any chin) + phasic TA	4	0.873 (0.780–0.938)	0.956 (0.901–0.986)	137.48 (27.501–687.33)	0.9642
Manual (any chin)	6	0.901 (0.845–0.942)	0.892 (0.840–0.932)	130.37 (30.735–552.97)	0.9657
Manual (phasic chin)	11	0.600 (0.546–0.652)	0.896 (0.859–0.927)	32.450 (12.173–86.502)	0.9348
Manual (tonic chin)	9	0.823 (0.775–0.864)	0.937 (0.900–0.963)	66.966 (25.644–174.87)	0.9546
Automatic RAI	7	0.891 (0.846–0.927)	0.735 (0.678–0.787)	43.061 (13.302–139.40)	0.9369

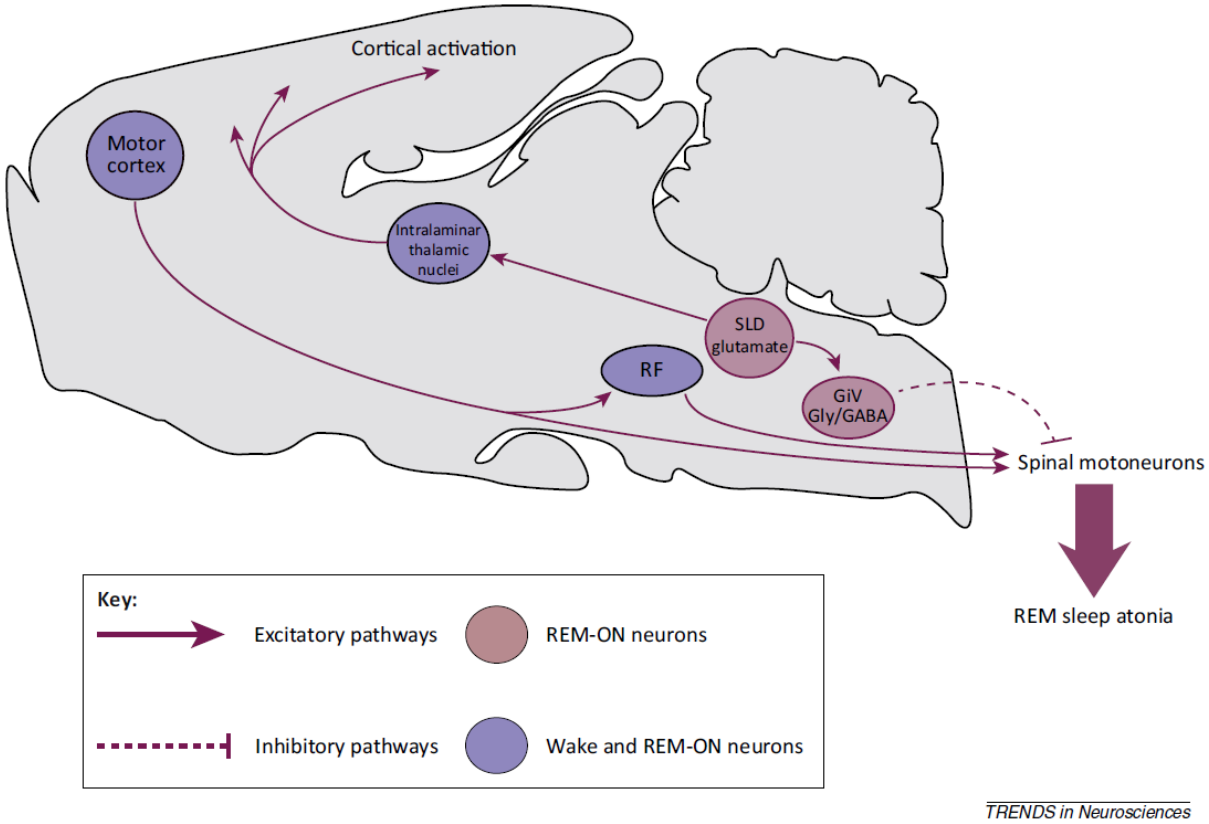
➔ manual RWA quantification that employed chin or phasic FDS activity had the best RBD diagnostic performance.
➔ The automatic RAI method may be useful for screening patients with RBD.

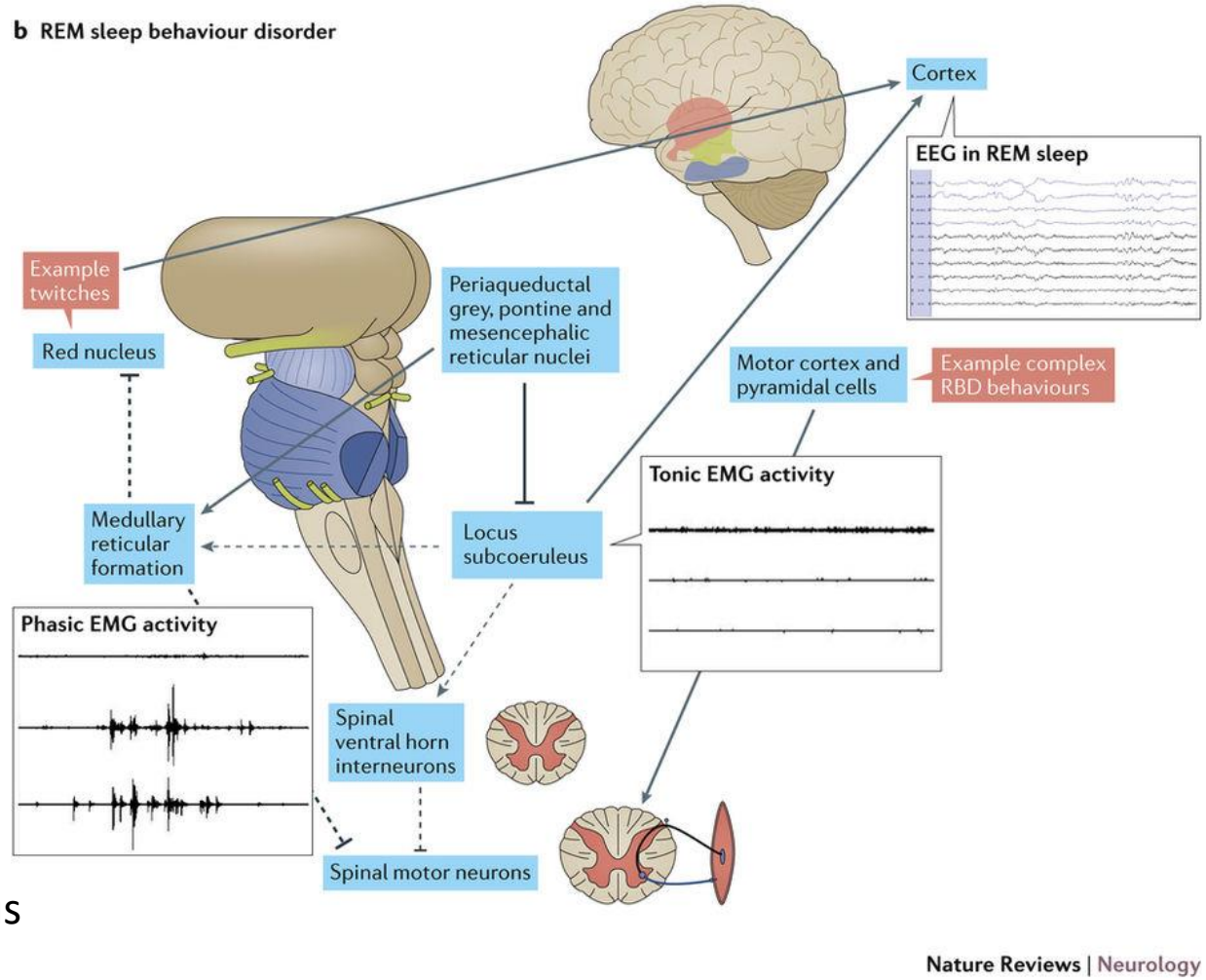
SLEEP 2022

Discussion

- Diagnostic performance of all RWA quantification methods, with AUC values above 0.9. **Overall, manual scoring of any chin and phasic FDS activity was the best for RBD diagnosis**.
- Applying **any chin activity alone showed an overall convincing sensitivity and specificity achieving 90%.**
- Additional use of phasic FDS activity increased the sensitivity (90.1%-> 93.1%), specificity (89.2%->91.3%), DOR (130.37->138.80), and AUC (0.9657->0.9686).
- **employing an additional phasic limb muscle, regardless of whether it is the FDS or TA, may increase the diagnostic performance of RBD compared with assessing chin activity alone.**
- **The RAI method has adequate sensitivity despite its limited specificity. could be a useful screening tool for RBD**

Pathophysiology

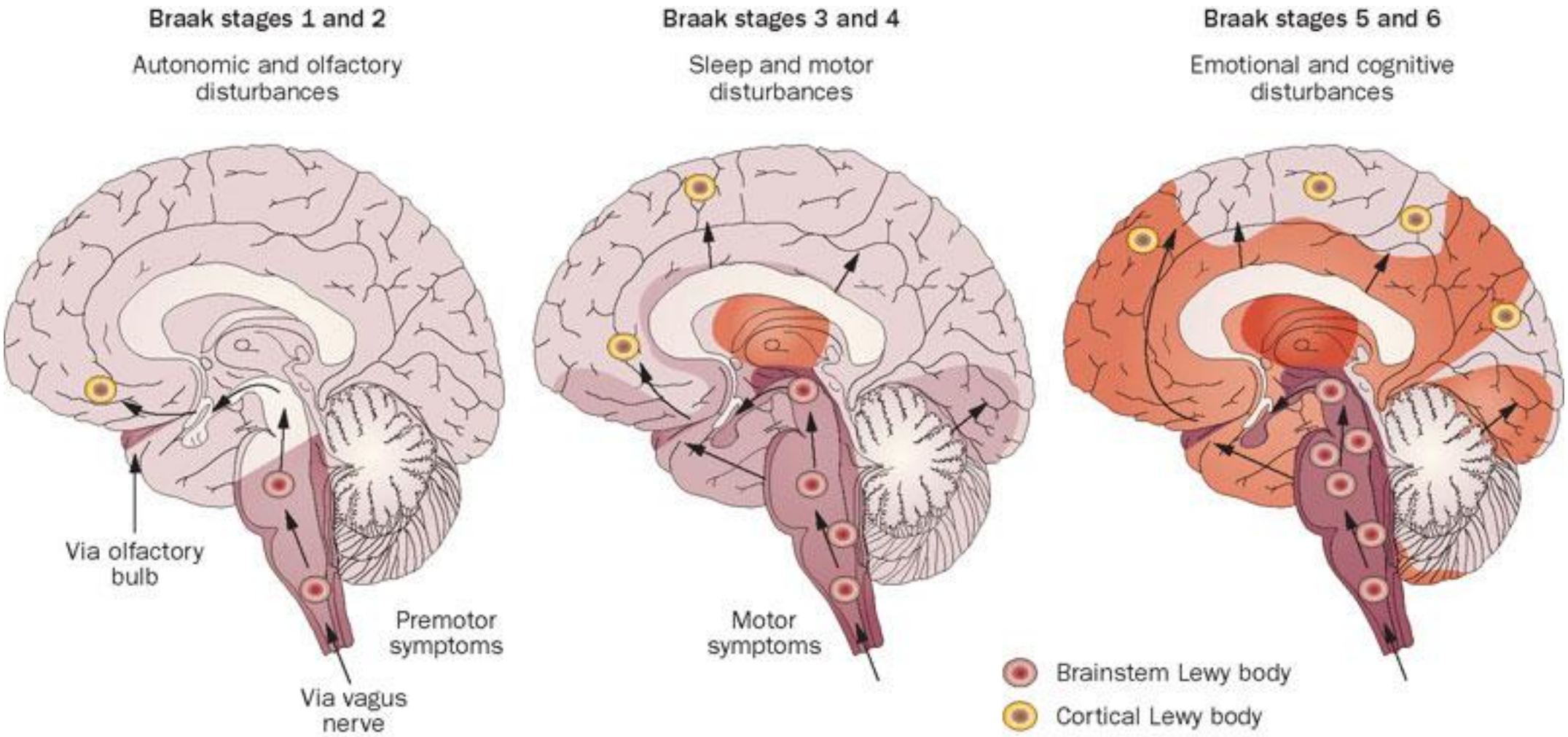




- **Tonic activity**: degeneration of the sublaterodorsal (SLD) nucleus
- **Phasic activity**: alteration of pathways in the intermediate ventromedial medulla

Hogl et al *Nat Rev Neurol* 2017

Braak Hypothesis



Quantitative network comparisons of REM sleep without atonia across the α-synucleinopathy spectrum: A systematic review

- There is lack of integrated and systematic evidence to inform the relative difference in the **percentage of tonic chin RWA (pRWA-T) or the percentage of phasic chin RWA (pRWA-P)** during REM sleep among the prodromal and overt α-synucleinopathy phenotypes. Only a few studies directly compared the severity of REM atonia loss between the two or more groups.
- **In this systematic review, we adopted the NMA approach to compare the group difference by combining direct and indirect evidence within a network of reported studies.**
- Comparison of the pRWA-T or pRWA-P between or within the α-synucleinopathy phenotypes could be valuable to evaluated the significance of RWA according to the neurodegenerative process.
- The comparison may not only reveal different patho-mechanism, but also have diagnostic value in differentiating one from another.

Methods

- The protocol of this study was specified in advance and was registered in PROSPERO (Registration No. CRD42021277446).
- **Inclusion criteria:** studies that provided information for the **manual scoring of tonic or phasic chin RWA percentage values in two or more groups of α-synucleinopathy phenotypes**.
- Mean group difference of pRWA-T and pRWA-P between or within α-synucleinopathy phenotypes were the outcome in this review.
- Effect size was obtained as means and standard deviations from the primary studies.

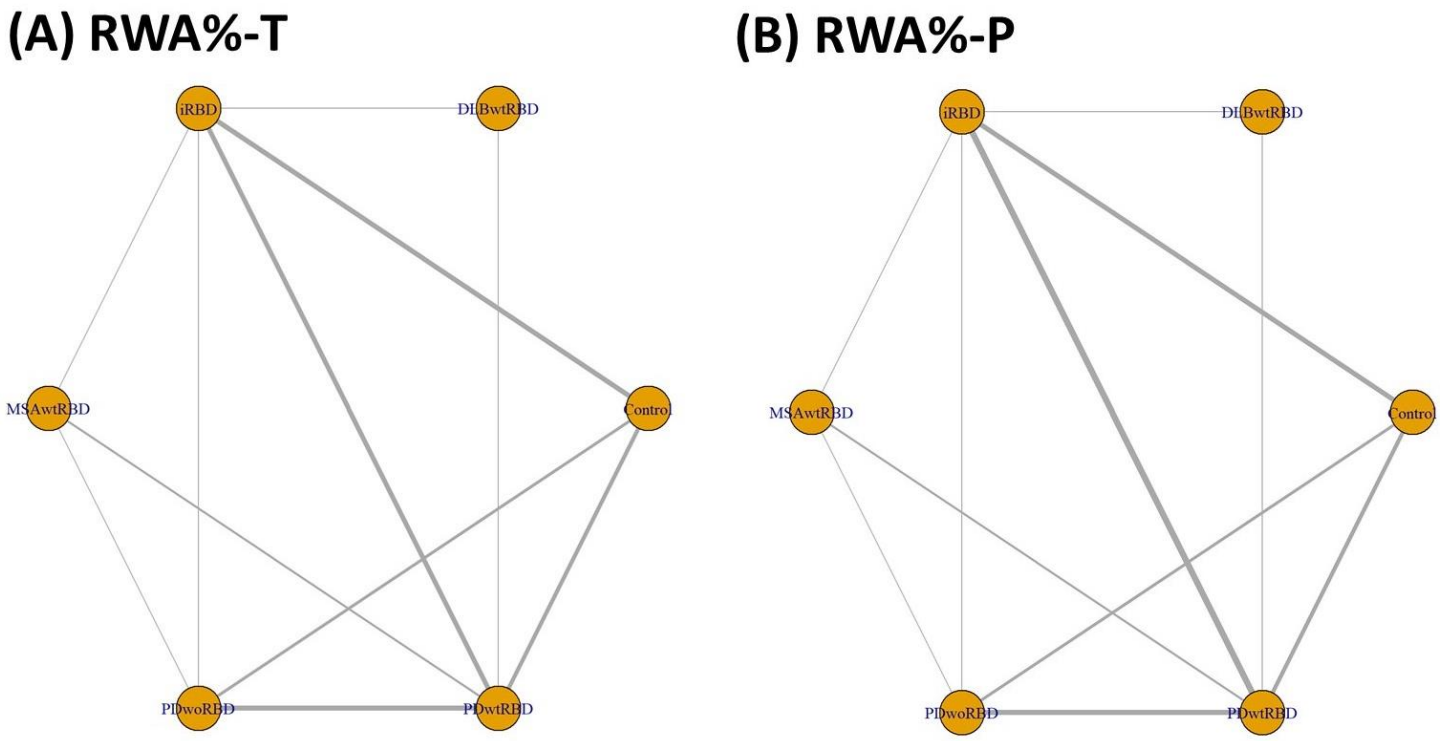
- first performed pairwise meta-analysis for pRWA-T or pRWA-P between groups using a random-effect model

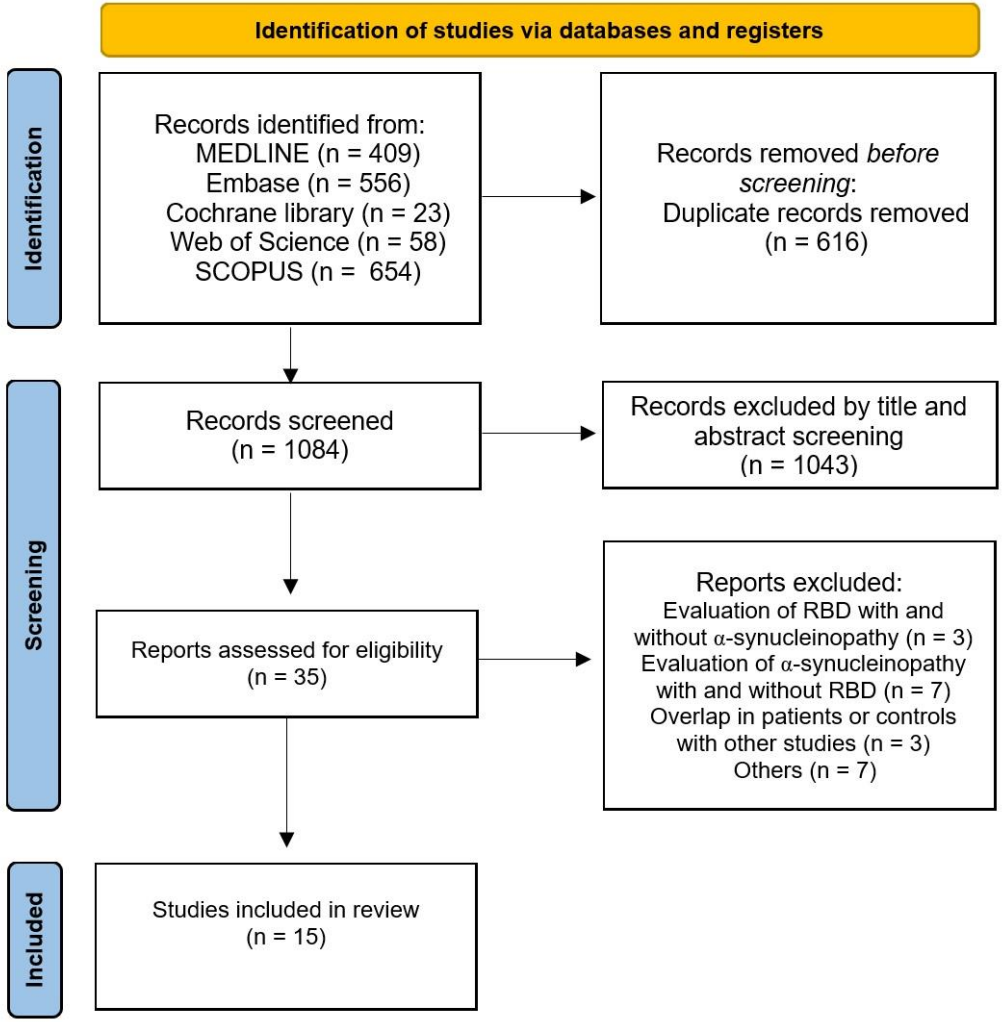
- than performed **NMA using a Bayesian framework random-effect model** (4 chain, adaptive phase 500, sampling phase 10000 iteration) to compare between or within the α-synucleinopathies spectrum.

- ranking probabilities using the **surface under the cumulative ranking curve (SUCRA)**

Results

15 studies (204 iRBD, 295 PDwtRBD, 187 PDwoRBD, 42 MSAwtRBD, 9 DLBwtRBD, 246 HC)



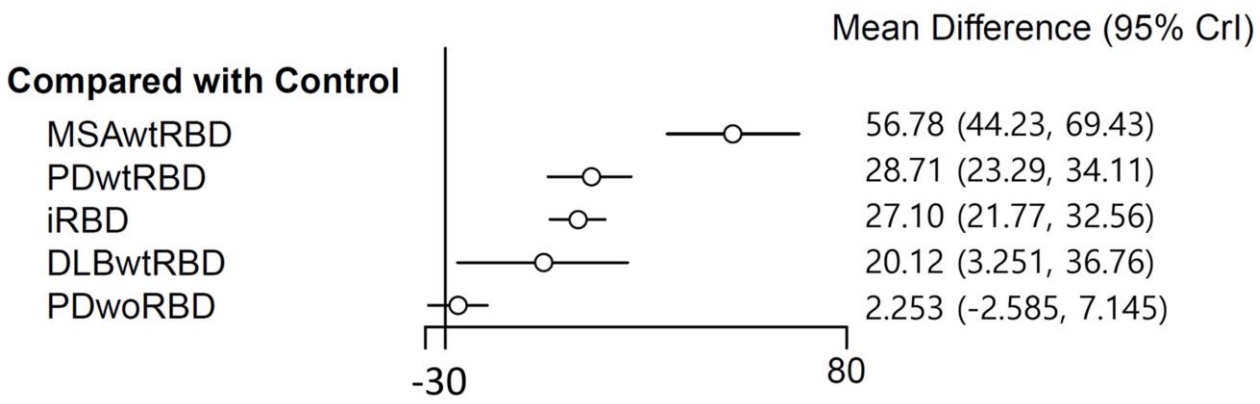


Results: pair-wise, network meta-analysis

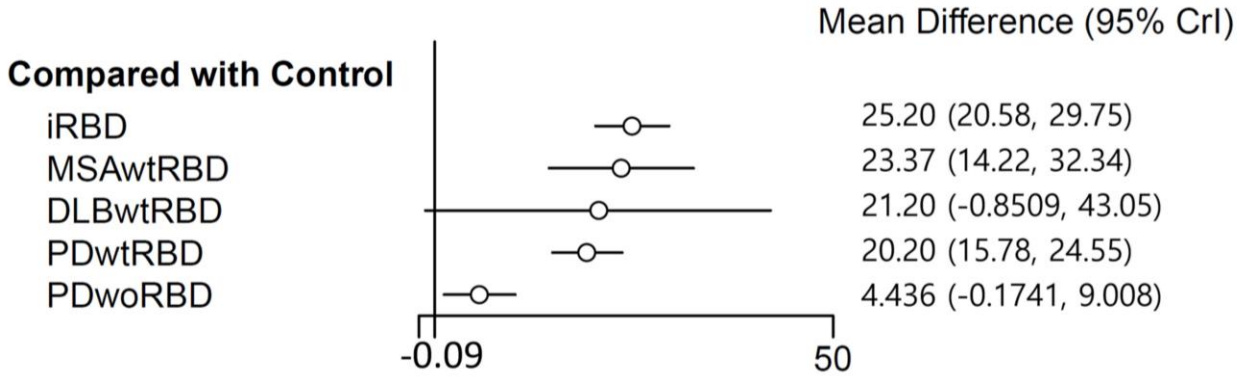
Supplementary Table 3. Summary estimates from pair-wise meta-analyses of direct comparisons in RWA%-T and RWA%-P.

	Mean difference in RWA%-T MD (95% CI)	Mean difference in RWA%-P MD (95% CI)
iRBD vs Controls	**31.40 (16.24, 46.55)**	**25.24 (19.31, 31.17)**
PDwoRBD vs Controls	0.92 (-1.16, 3.00)	1.78 (-4.79, 8.34)
PDwtRBD vs Controls	**33.81 (13.91, 53.72)**	**24.42 (14.37, 34.48)**
PDwtRBD vs PDwoRBD	**23.47 (9.34, 37.60)**	**14.95 (4.78, 25.12)**
PDwtRBD vs iRBD	6.17 (-13.99, 26.32)	-6.16 (-14.93, 2.60)

(A) RWA%-T



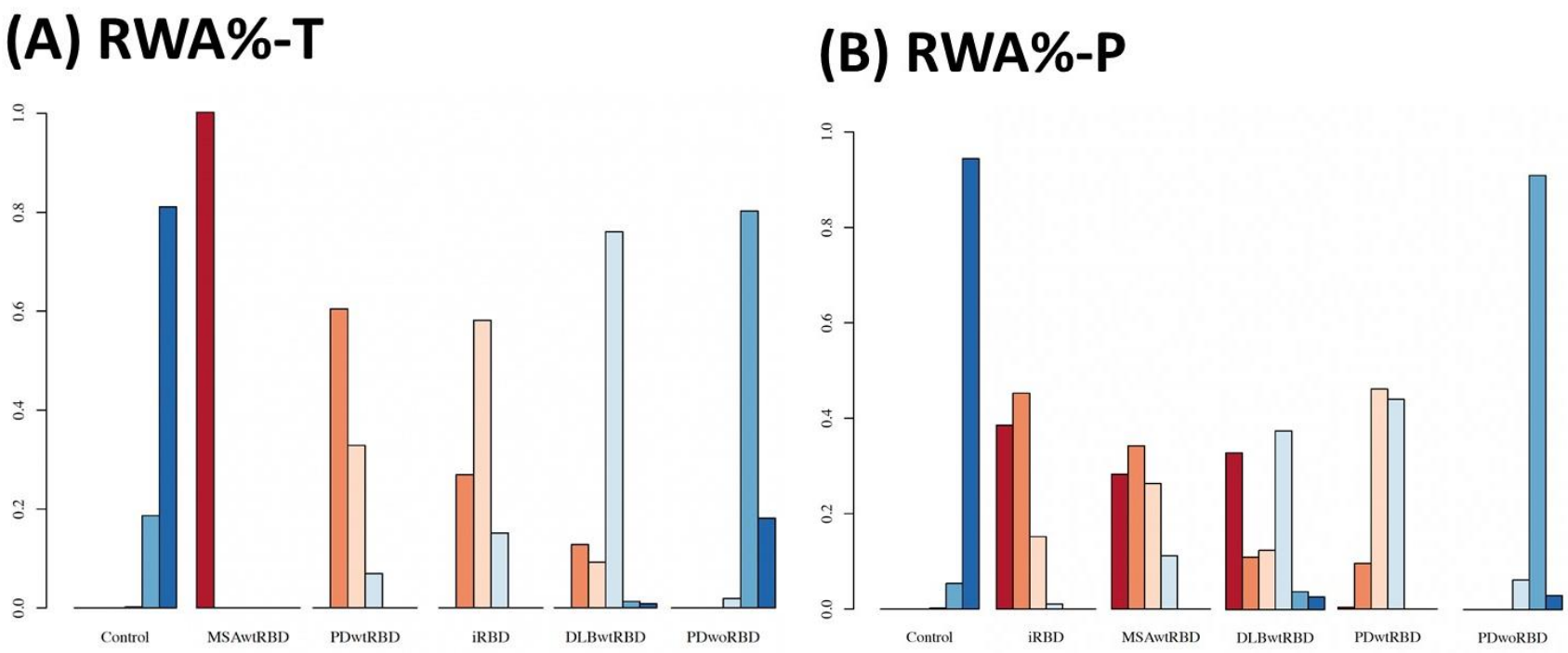
(B) RWA%-P



Results: SUCRA

Supplementary Table 6. Rank probabilities

Phenotypes	RWA%-T	RWA%-P
MSAwtRBD	1.000	0.742
PDwtRBD	0.709	0.543
DLBwtRBD	0.465	0.639
PDwoRBD	0.168	0.209
iRBD	0.621	0.855
Controls	0.038	0.012



- MSAwtRBD ranked first in RWA%-T, whereas iRBD ranked first in RWA%-P.
- RWA% in PDwoRBD patients was comparable to the controls and was lower than that in PDwtRBD.

Discussion

- pRWA-T was highest in patients with MSAwtRBD followed by PDwtRBD, iRBD, and DLBwtRBD.
- pRWA-P was highest in iRBD group, followed by MSAwtRBD, DLBwtRBD, and PDwtRBD.

- suggests that **pRWA-T is associated with the neurodegeneration** of α-synucleinopathy.

- lack of association between pRWA-P and neurodegenerative process

- **MSAwtRBD had the highest pRWA-T**

- Diffuse involvement of brainstem in MSA may have resulted higher pRWA-T

- Increase in pRWA-T may aid differentiating MSAwtRBD from PDwtRBD patients.

- **DLBwtRBD ranked lower than the iRBD or PDwtRBD**

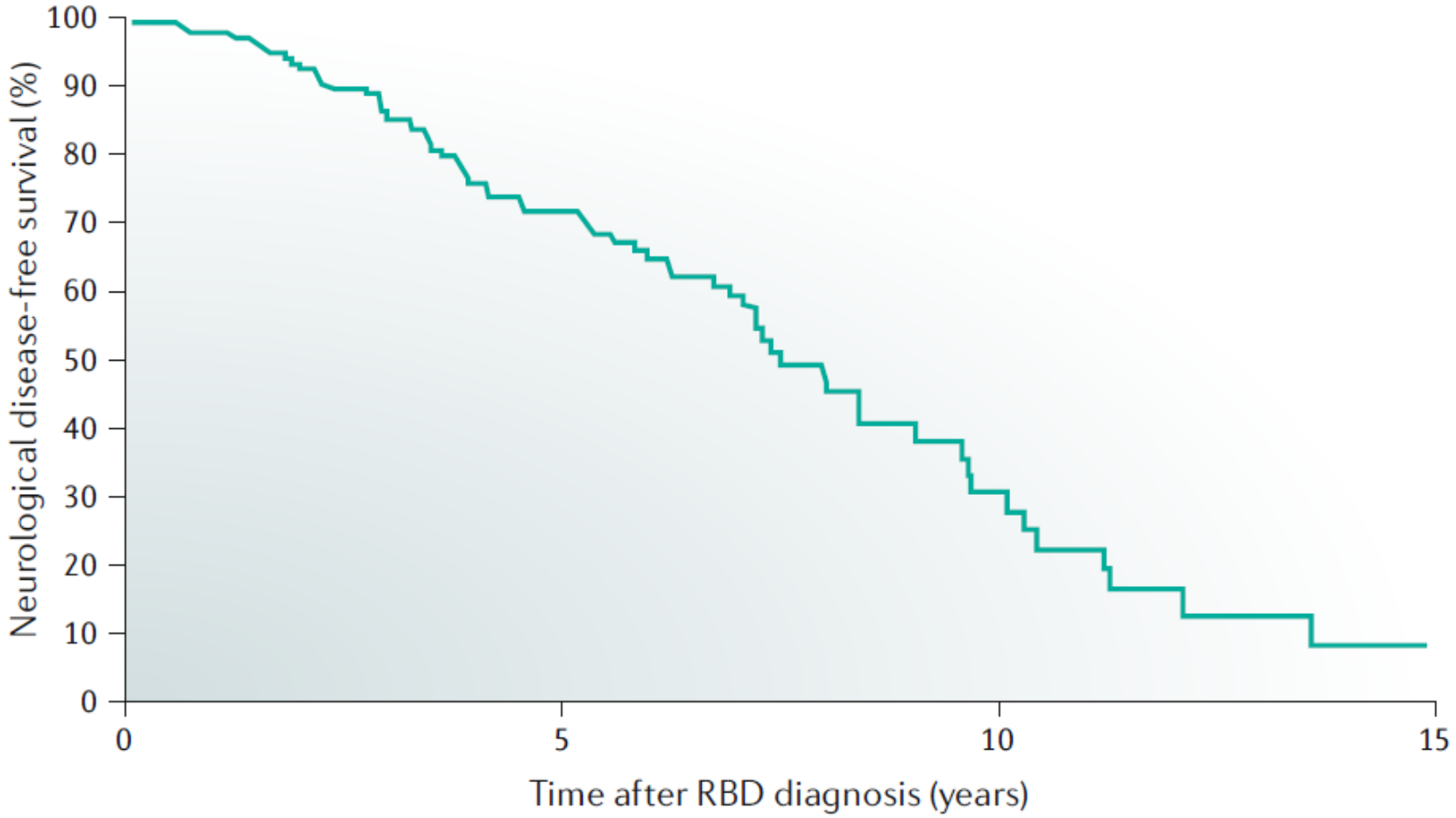
- Statistics: one included study dealt with DLBwtRBD data (n=9)

- Lewy body pathology in DLB may initially appears in the brain, then spreads to the brainstem

- pRWA-T linked to the risk for PD but not dementia

RBD and Neurodegeneration

- **Strongly associated with synucleinopathy neurodegeneration**
- 33.1% (5 years), **75.7% (10 years), 90.9% (14 years)**



Nat Review, 2018

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

Ronald B. Postuma,[1,2] Alex Iranzo,[3] Michele Hu,[4] Birgit Högl,[5] Bradley F. Boeve,[6] Raffaele Manni,[7] Wolfgang H. Oertel,[8] Isabelle Arnulf,[9] Luigi Ferini-Strambi,[10] Monica Puligheddu,[11] Elena Antelmi,[12,13] Valerie Cochen De Cock,[14] Dario Arnaldi,[15] Brit Mollenhauer,[16] Aleksandar Videnovic,[17] Karel Sonka,[18] Ki-Young Jung,[19] Dieter Kunz,[20] Yves Dauvilliers,[21] Federica Provini,[22,23] Simon J. Lewis,[24] Jitka Buskova,[25] Milena Pavlova,[26] Anna Heidbreder,[27] Jacques Y. Montplaisir,[2] Joan Santamaria,[14] Thomas R. Barber,[4] Ambra Stefani,[5] Erik K. St.Louis,[6] Michele Terzaghi,[7] Annette Janzen,[8] Smandra Leu-Semenescu,[9] Guiseppe Plazzi,[12,13] Flavio Nobili,[15] Friederike Sixel-Doering,[16] Petr Dusek,[18] Frederik Bes,[20] Pietro Cortelli,[22,23] Kaylena Ehgoetz Martens,[24] Jean-Francois Gagnon,[28] Carles Gaig,[3] Marco Zucconi,[10] Claudia Trenkwalder,[15] Ziv Gan-Or,[29,30] Christine Lo,[4] Michal Rolinski,[4] Philip Mahlknecht,[5] Evi Holzknecht,[5] Angel R. Boeve,[6] Luke N. Teigen,[6] Gianpaolo Toscano,[7] Geert Mayer,[31] Silvia Morbelli,[32] Benjamin Dawson,[1] Amelie Pelletier[1,2] and the International REM Sleep Behavior Disorder Study Group

- 1280 patients from 24 centers of IRBDSG.
- Average follow-up **4.6 years (1-19 years)**
- conversion rate **6.3%/yr**

  (73.5% converting after 12-year follow-up).

Increase risk of conversion

- abnormal quantitative **motor testing** [hazard ratio (HR) = 3.16]
- objective motor examination (HR = 3.03)
- **olfactory deficit** (HR = 2.62)
- **mild cognitive impairment** (HR = 1.91-2.37)
- erectile dysfunction (HR = 2.13)
- motor symptoms (HR = 2.11)
- abnormal DAT scan (HR = 1.98)
- colour vision abnormalities (HR = 1.69)
- constipation (HR = 1.67)
- **REM atonia loss (HR = 1.54)**
- age (HR = 1.54).

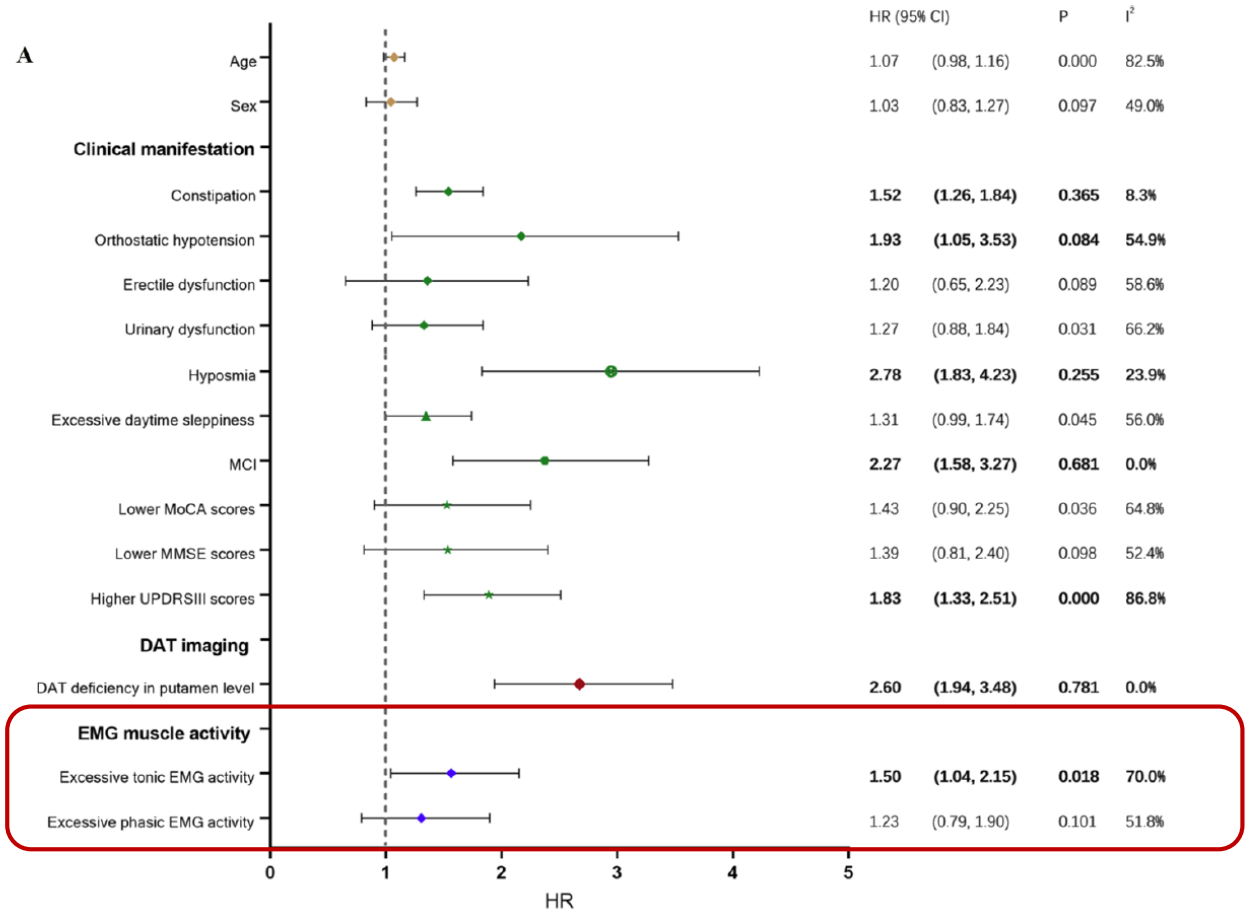
Brain, 2019

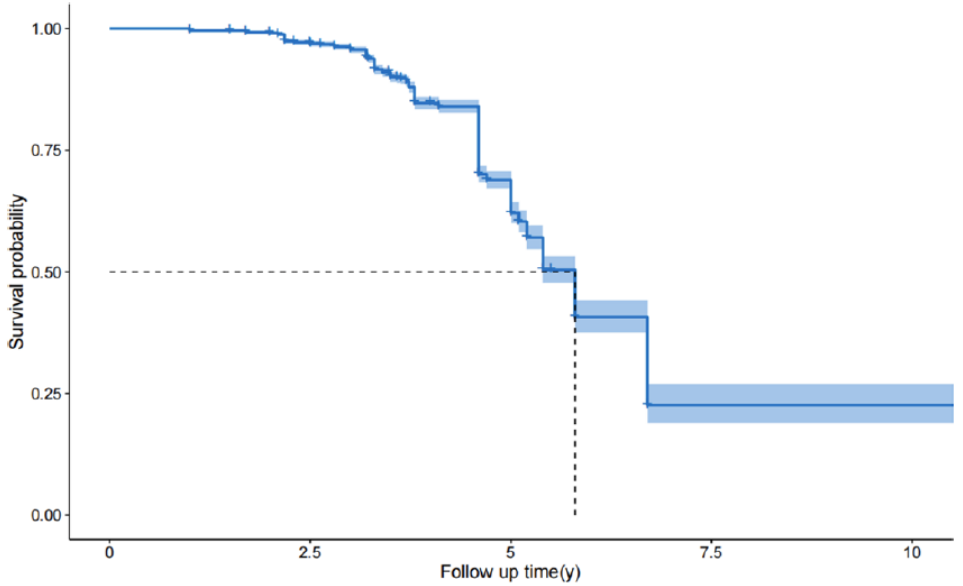
Possible predictors of phenoconversion in isolated REM sleep behaviour disorder: a systematic review and meta-analysis

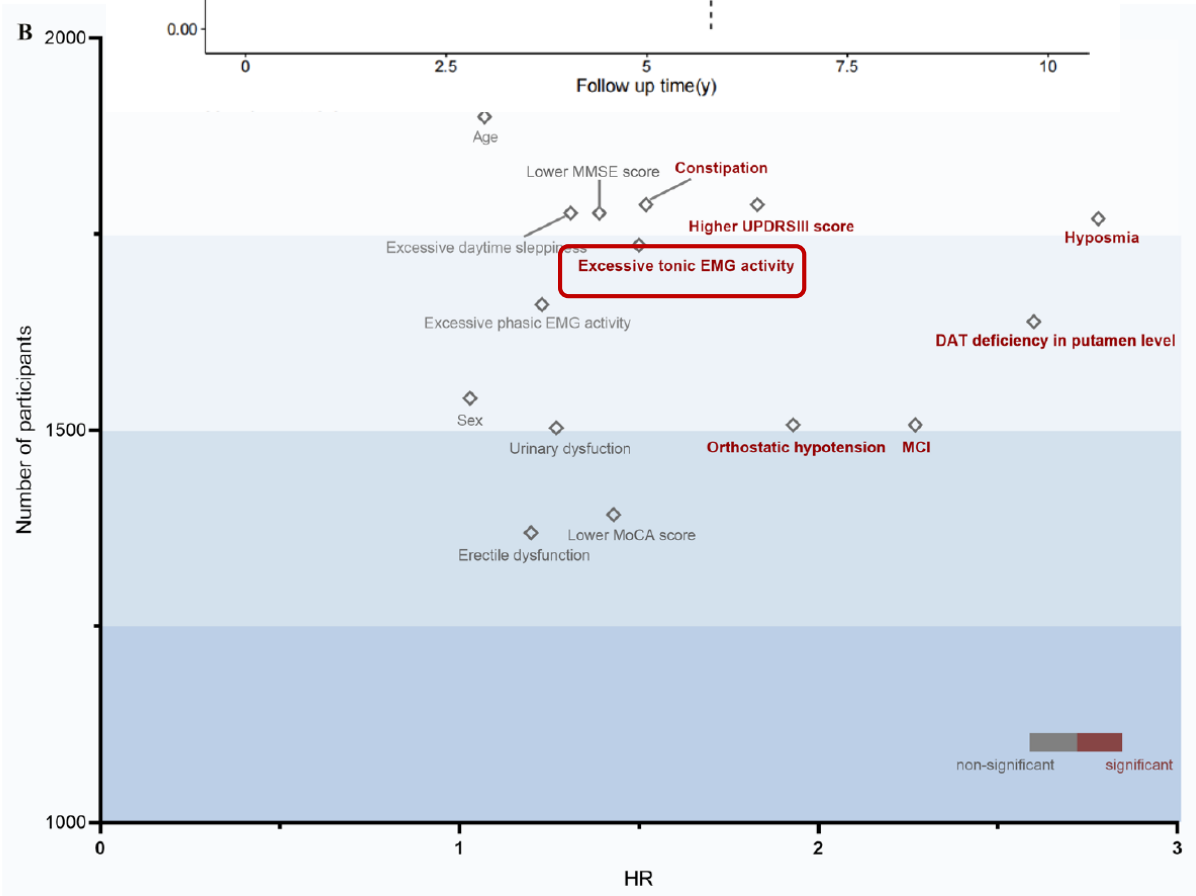
Chunyi Wang,[1] Fangzheng Chen,[1] Yuanyuan Li ,[1] Jun Liu [1,2,3]

JNNP 2022

- 123 studies with total of 10515 participants (3582 IRBD, 3410 HC, 737 PD with RBD, 2786 PD without RBD)







Summary

- Manual method using **chin and phasic FDS activity is the best RWA quantification method for RBD diagnosis**.
- The automatic **RAI method can be used as a screening tool** to diagnose RBD before manual methods are performed to confirm the diagnosis.
- Difference in the ranks order between the pRWA-T and pRWA-P may be due to different patho-mechanism

- pRWA-T is associated with degeneration of the sublaterodorsal nucleus

- pRWA-P is associates with changes of intermediate ventromedial medulla pathways

- The **neurodegenerative process was linked to pRWA-T**, which was highest in MSAwtRBD
- pRWA-P was highest in iRBD, so it might not be associated with neurodegenerative process.