

Diagnostic Challenges of Pediatric Hypersomnia Disorders

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Disclosures



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Hypersomnia Conditions Commonly Begin Before 18 Years of Age

Narcolepsy type 1 and 2

- Symptom onset is typically begin between ages 10-20 years (peak 15 years)
- Up to 50% of patients with narcolepsy diagnosed as adults recall symptoms before age 18 years
- Survey data from Unite Narcolepsy (n=1386)
 - 39.2% reported symptom onset before age 18 years
 - 60.8% reported symptom onset at 18 years of age or older

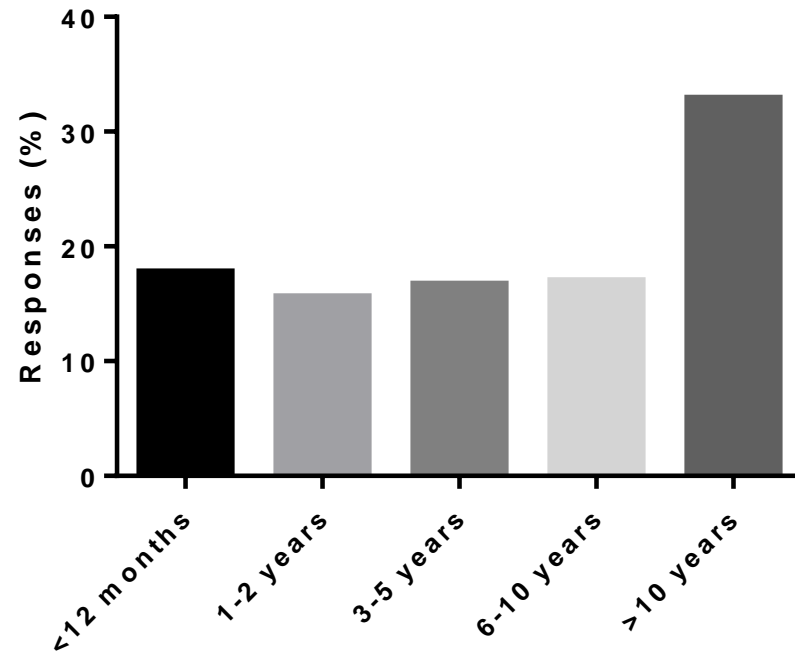
Data on other pediatric hypersomnia conditions (IH) are sparse

- Survey data from Unite Narcolepsy of people reporting “other hypersomnia conditions” (n=121)
 - 52.3% reported symptom onset before age 18 years
 - 47.7% reported symptom onset at 18 years of age or older

Thorpy MJ Neurology 1999; Sleep Med, 2014
Maski K et al. JCSM 2017

Narcolepsy Diagnostic Delays

Time From Symptom Onset to Diagnosis of Narcolepsy
(N=1451)



**About 50% patients
report >5 year diagnostic delay**

Factors that contribute to delay

- Pediatric onset of symptoms (OR=2.4)
- No cataplexy (OR=1.8)

Unite Narcolepsy survey of n=1699 patients with narcolepsy in United States. OR data
adjusted for current age

Maski K et al. JCSM 2017

Misdiagnosis is Common

Patients with narcolepsy are 4 times more likely than other patients to receive a misdiagnosis including:

- Mental health problem
- Epilepsy
- Insomnia/other sleep disorder
- Lack of awareness by healthcare providers

Reasons misdiagnosis is prevalent

- 39% of PCP could identify narcolepsy symptoms
- Symptoms overlap with other more common sleep, medical and psychiatric conditions
- Excessive daytime sleepiness (EDS)/fatigue is reported by 25% of school aged children due to insufficient sleep
- EDS may manifest as attention problems, memory issues, hyperactivity, behavior problems especially in children
- Race may affect presentation

Thorpy MJ, 2014; Rosenberg R, 2014; Ohayon MM SLEEP 2013; Carter LP Postgrad 2014

Race Influences Disease Presentation

In a cohort study, African Americans (n=182):

- have lower levels of CSF hypocretin [19.4 pg/ml] vs. other ethnic groups [60-127 pg/ml]
- have worse subjective sleepiness (ESS 19 vs. 17-18)
- Have earlier presentation of sleepiness (13 years) vs. Caucasians (18 years)
- Have less reporting of frequent cataplexy compared to Caucasians (71% vs. 91%) even with hypocretin <110 pg/ml

What About Diagnostic Delays in Other Hypersomnia Conditions?

- **Misdiagnosis is common**
 - Depression
 - OSA
 - Narcolepsy
- **Based on Unite Narcolepsy survey data of patients reporting other chronic hypersomnia conditions (n=318)**
 - 31.8% of respondents reported >5 year delay in diagnosis from symptom onset

Diagnosing Narcolepsy

Narcolepsy Type 1 (Narcolepsy with Cataplexy). A and B must be met

- A. EDS for at least 3 months.
 - Validated questionnaires encouraged such as Epworth Sleepiness Scale-CHAD
- B. At least **one** of the following:
 - Cataplexy and a positive Multiple Sleep Latency Test (MSLT)*
 - Low CSF hypocretin-1 concentrations (≤ 110 pg/ml or $< 1/3$ of normal)

Narcolepsy Type 2 (Narcolepsy without Cataplexy). A and B must be met

- A. EDS for at least 3 months.
- A. Positive MSLT*

***Positive MSLT:** mean sleep latency of ≤ 8 minutes and ≥ 2 SOREMPs* .
A SOREMP on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

International Classification of Sleep Disorders version 3

*SOREMP=sleep onset REM periods (REM sleep within 15 minutes from sleep onset latency)

Diagnosis of Idiopathic Hypersomnia

All of the following criteria must be met

1. Daily daytime sleepiness, defined as an “irrepressible need to sleep” or daytime sleep, that has been present at least 3 months
2. No cataplexy
3. No MSLT evidence for narcolepsy (ie, <2 sleep-onset REM periods on the overnight PSG and daytime MSLT considered together)
4. Electrophysiologic evidence of hypersomnolence, defined as either (or both) of:
 - a. Mean sleep latency on MSLT of at least 8 minutes
 - b. At least 11 hours of sleep per 24 hours, documented on a single 24-hour PSG or averaged across at least 7 days of actigraphic monitoring during ad lib sleep

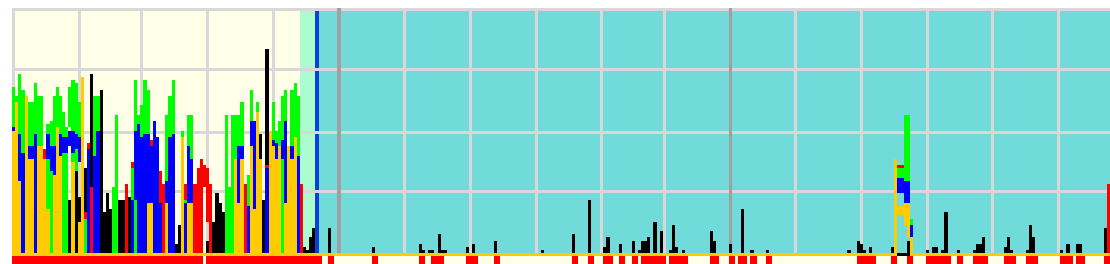
5. Insufficient sleep is ruled out (including immediately before 24-hour PSG, if performed)
6. No other disorder or substance use better explains the symptoms

Abbreviations: MSLT, multiple sleep latency test; PSG, polysomnogram; REM, rapid eye movement.

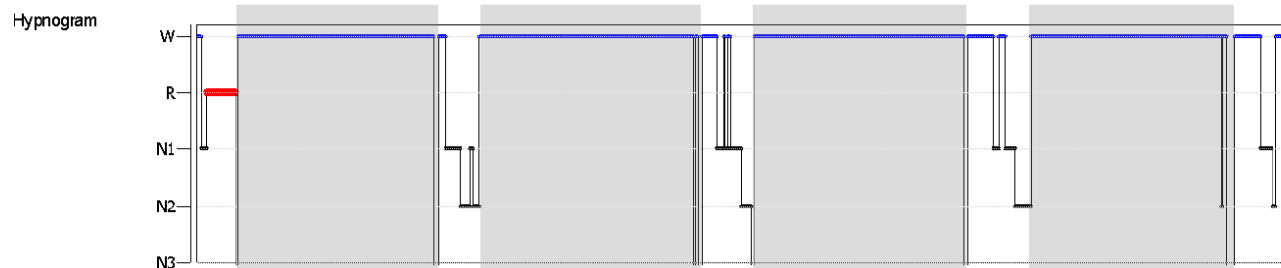
Data from International classification of sleep disorders. 3rd edition. Darien (IL): American Academy of Sleep Medicine; 2014.

IH Diagnostic Testing Options

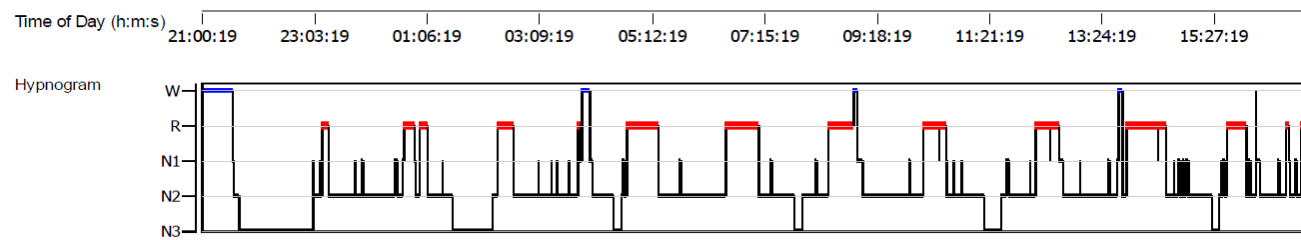
Actigraphy



MSLT (multiple sleep latency test)



Extended Polysomnogram



How Valid and Reliable is the MSLT for Narcolepsy Diagnosis?

False negative

1,180 patients with narcolepsy-cataplexy

- 4% of the sample had no SOREMPs during the MSLT
- 6% had only 1 SOREMP during a 5 naps MSLT

European Narcolepsy Network Study. Luca GL J Sleep Research 2013

False positive

1518 adults in Wisconsin Sleep Cohort Study

- 7% had multiple SOREMPs while the prevalence of MSL
- 22% had MSL < 8 min on the MSLT
- 3.4% had a combination of the two

Goldbart A et al SLEEP 2014

Likely Higher False Positives in Adolescents

Participants:

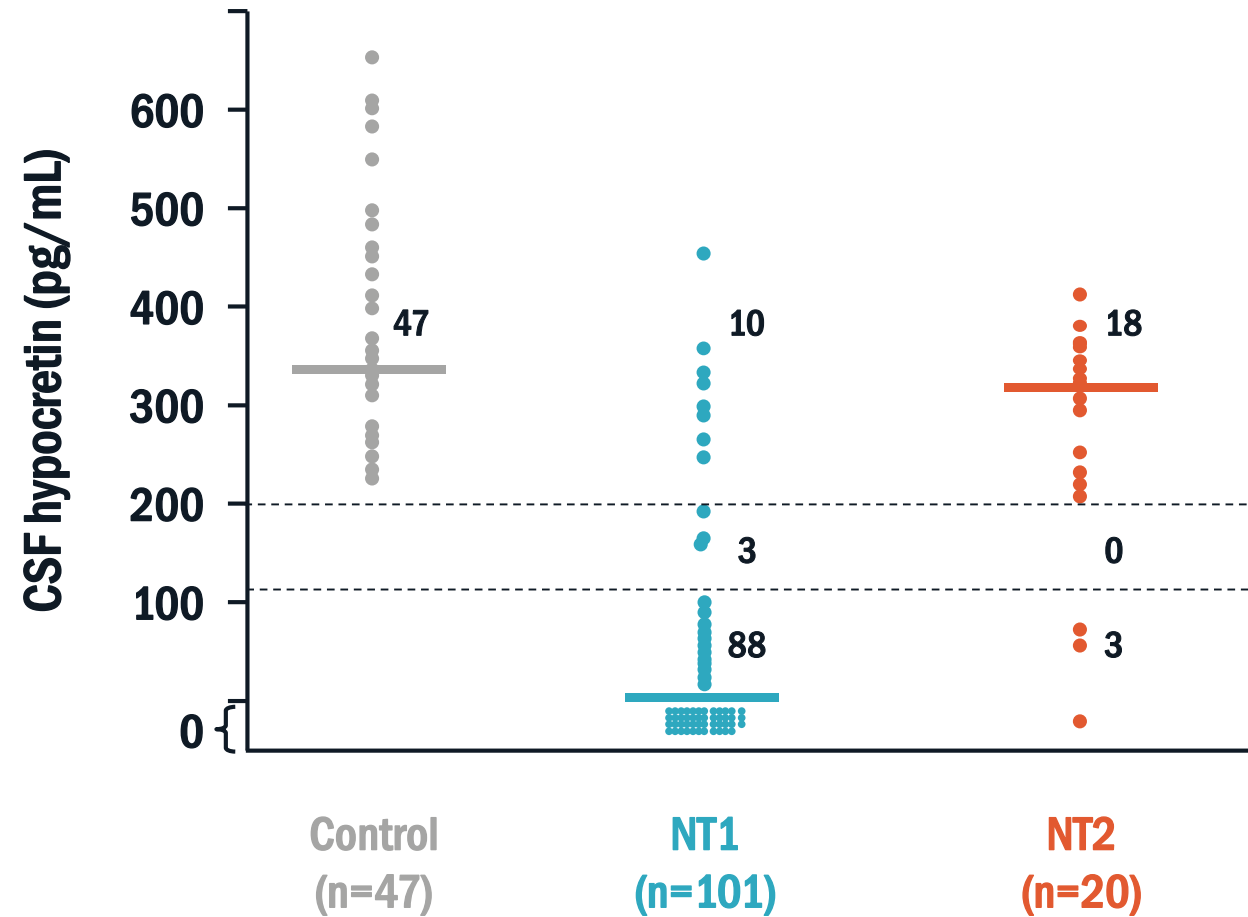
- 32 students in 9th grade (school start time 08:25)
- 26 students in 10th grade (school start time 07:20)
- Methods:
- 2 weeks of actigraphy followed by 22-hour in lab evaluation

Results:

- 10th grade students slept less and had later DLMO than 9th grade group
- 10th grade students had:
- mean MSL 8.5 minutes
- 16% had 2 SOREMPs
- 48% had 1 SOREMPs



Ideal Diagnostic Test for NT1 Would be CSF Hypocretin



Mignot E et al. Arch Neurol 2002



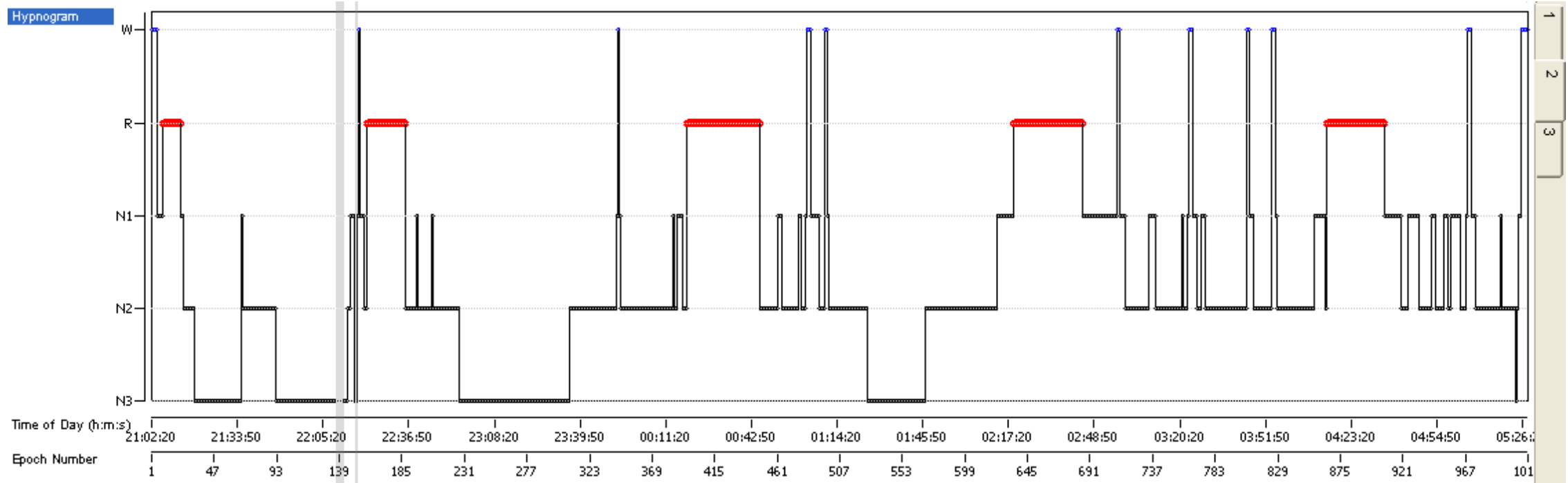
Neurophysiologic Diagnostic Biomarkers on Nocturnal Polysomnograms (PSG)

- **Biomarkers are characteristics that are objectively measured and evaluated as an indicator of pathogenic process**
 - Can be substance, structure or neurophysiological process that predict disease state or outcome
 - Can be useful for diagnosis, severity, predicted treatment response, prognosis
- **Sleep Neurophysiological Biomarkers Coupled with MSLT can improve diagnostic accuracy**
 - May be necessary as some insurances require a PSG alone be “normal” before PSG/MSLT permitted



Current Sleep Biomarkers for Narcolepsy Diagnosis: Rapid Transitions to REM Sleep

- Hypocretin regulates the REM sleep entry
- Low hypocretin levels result in early transitions to REM sleep
 - Nocturnal SOREMP (≤ 15 minutes from sleep onset)
 - Up to 97% specificity for NT1
 - Present in 50% of patients with NT1
 - Consistent in adults and children
 - Wake/stage 1 to REM sleep transitions
 - ≥ 5 epochs of Wake/N1 to ≥ 2 epochs of REM
 - Present in only 17% of patients with NT1
 - 100% specificity of NT1



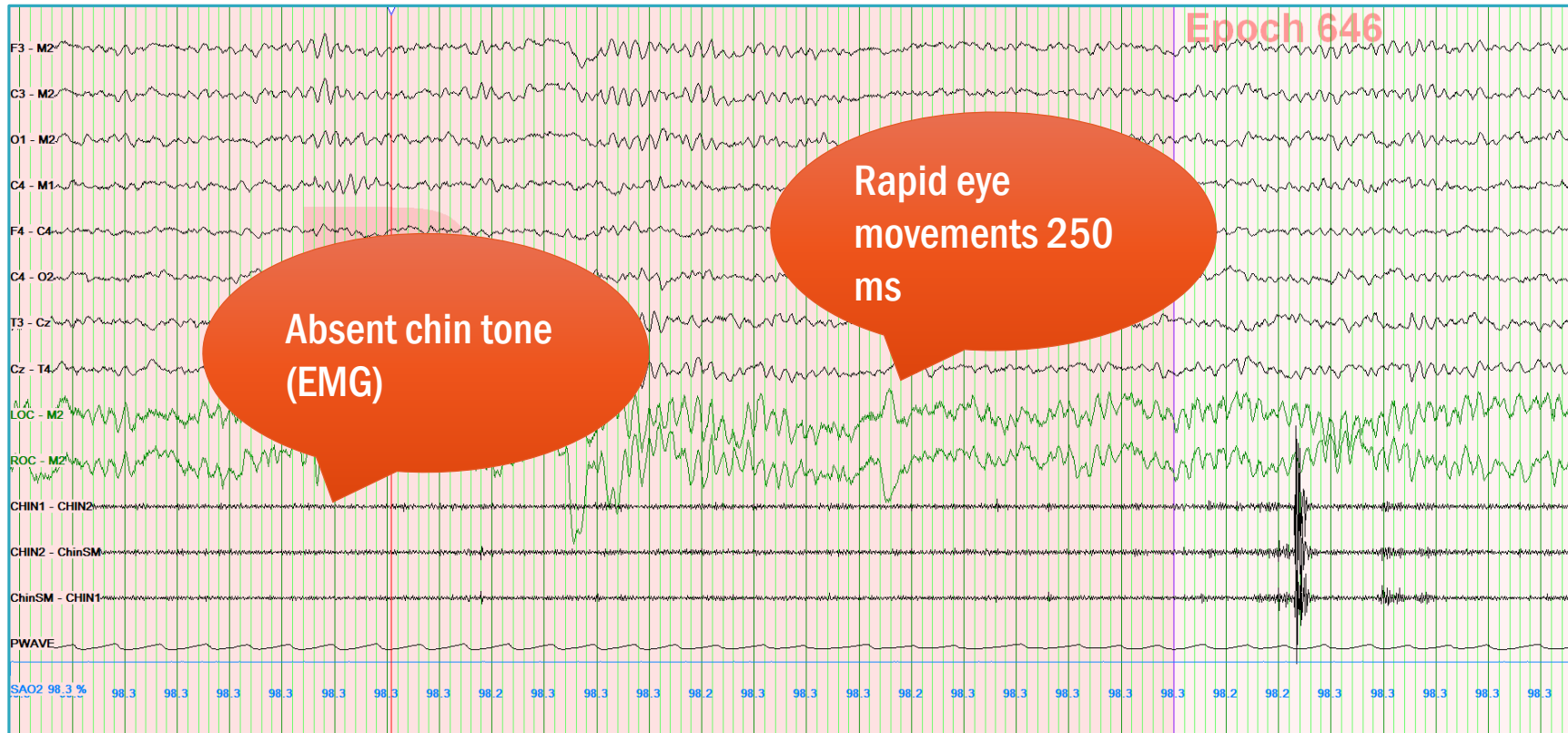
REM Without Atonia (RWA) as NT1 Diagnostic Biomarker

- **REM behavior disorder (20-36%)**
 - Up to 90% of adult patients with narcolepsy have REM without atonia on nocturnal polysomnography
 - REM without atonia (RWA) indices are 5-10x higher in narcolepsy patients compared to controls
 - Higher RWA indices correlate with lower hypocretin levels

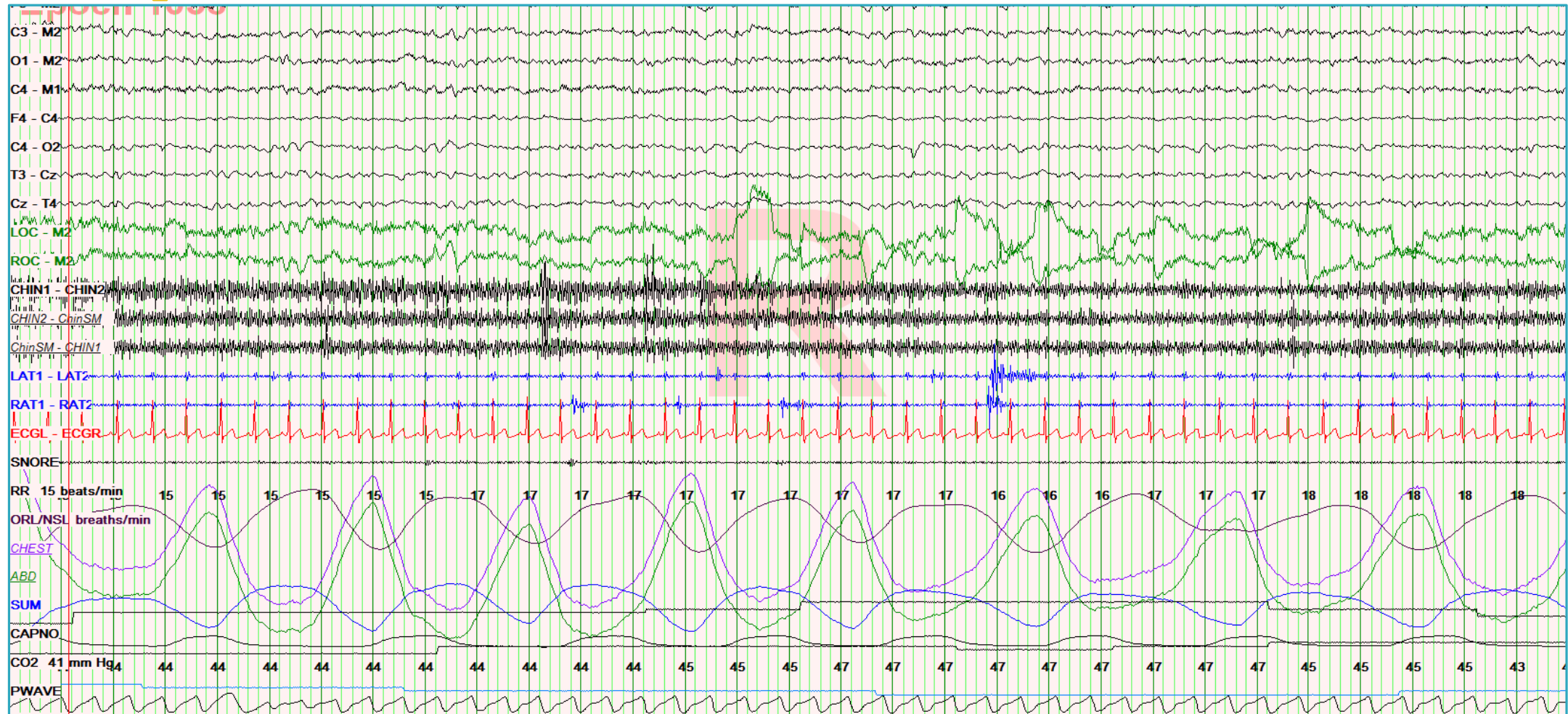
Roth T. JCSM 2013; Sasai-Sakuma PLoS One 2015; Wamsley E. SLEEP 2014; Antelmi E BRAIN 2017, Frauscher B JCSM 2013, Khalil A JCSM 2015, Olesen Sleep Med 2018

Normal REM Sleep

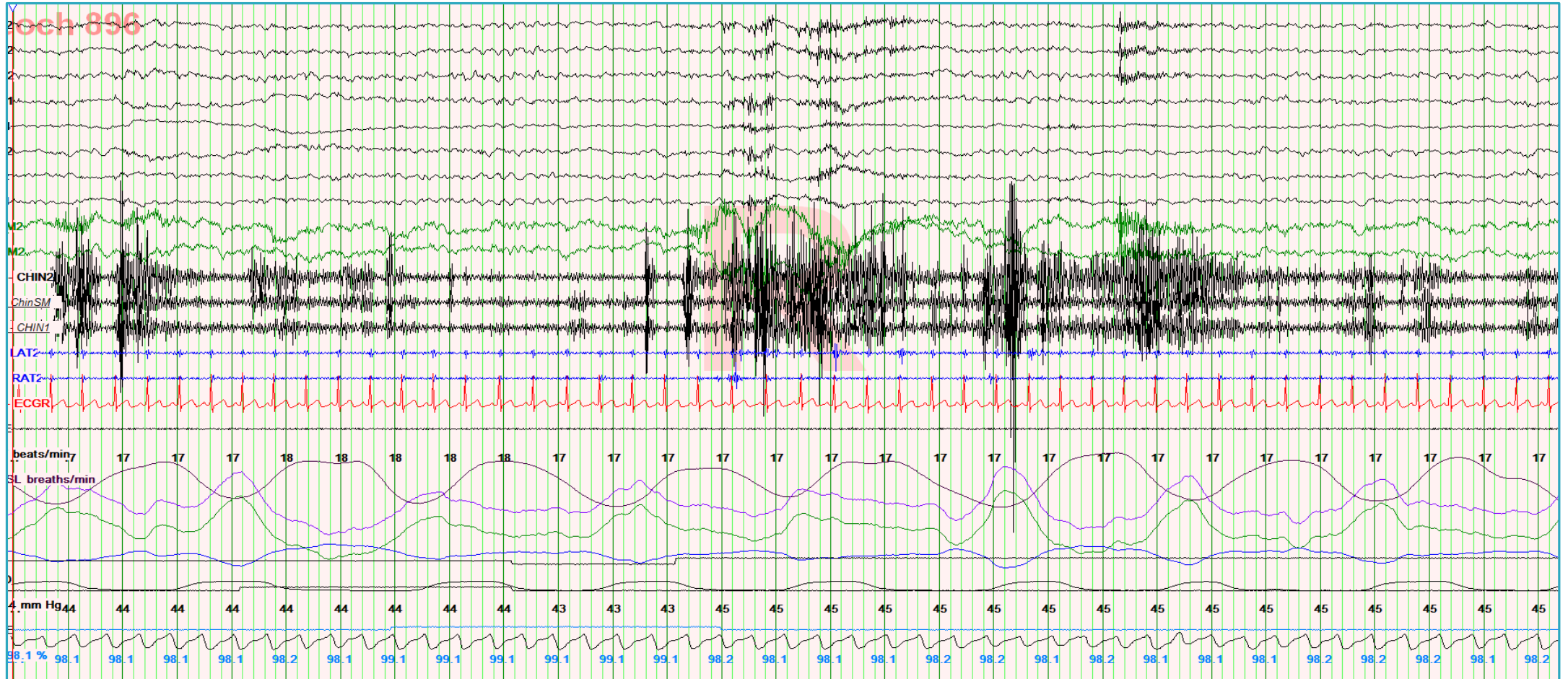
Mixed frequency EEG (low amplitude theta)



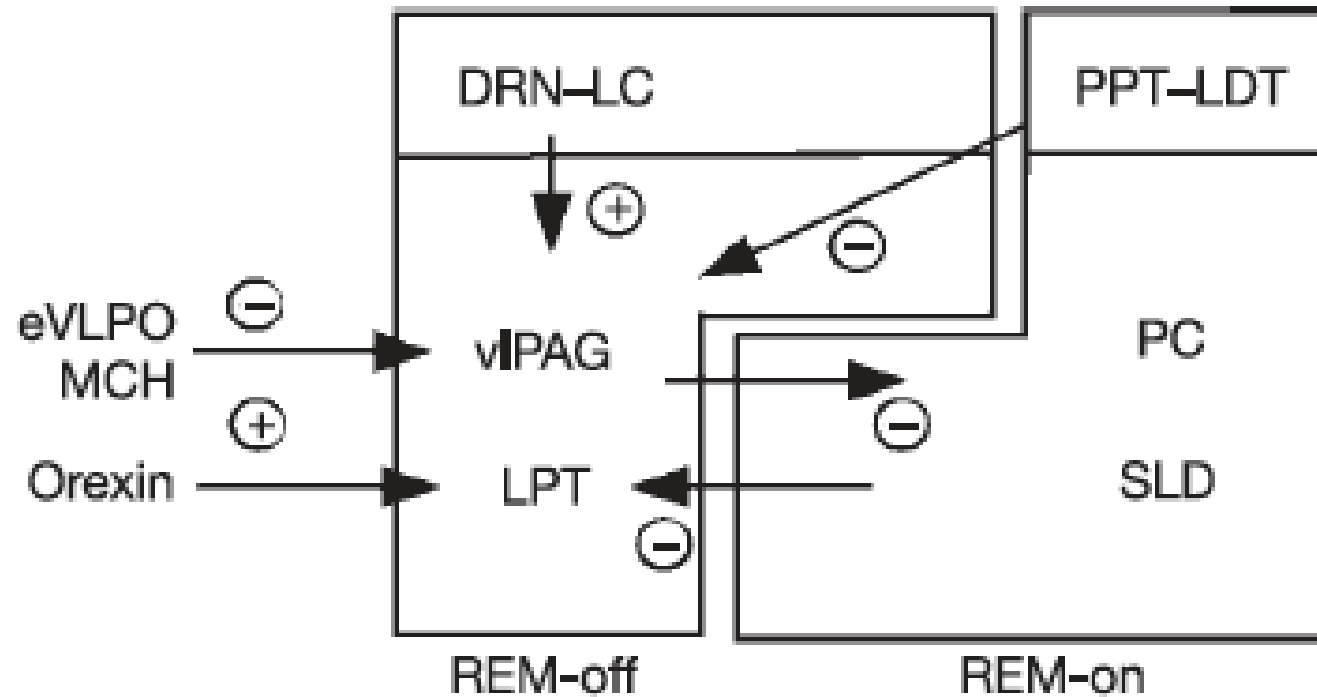
REM Tonic Activity: EMG Activity Comparable to NREM Sleep Present for 50% Of Epoch



REM Phasic Activity: 1/3 of epoch with EMG bursts of activity 4x higher than background



Orexin/hypocretin Regulates REM Off Neurons



Lu et al. Nature 2006

RWA Is A Diagnostic Biomarker of Pediatric Narcolepsy

40 drug naïve, aged 6-18 years consecutive patients having PSG/MSLT for eval of daytime sleepiness

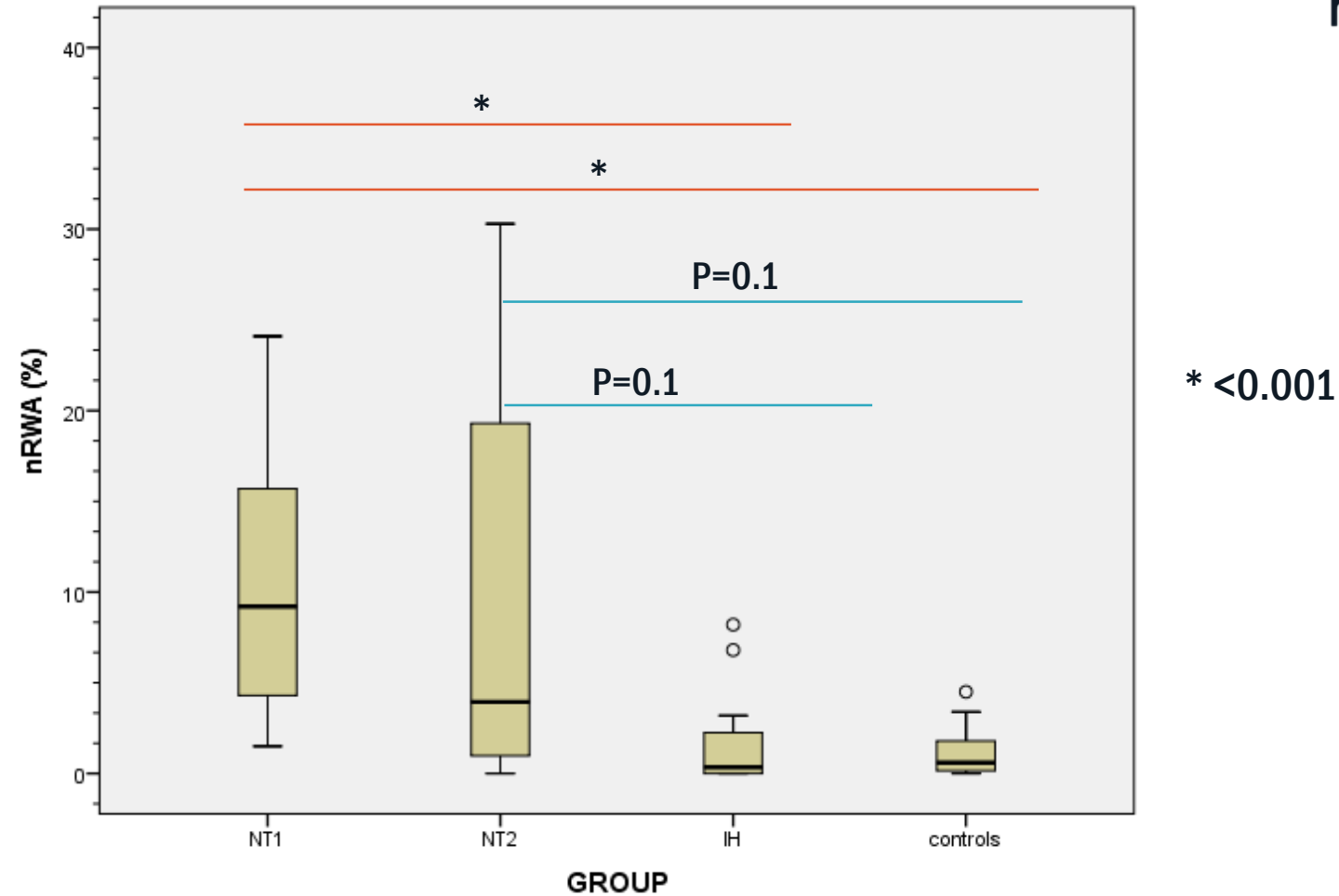
- NT1 (n=12), NT2 (n=6), IH (n=12), controls (n=11)

Methods:

- Scored REM sleep for RWA (tonic or phasic) based on American Academy of Sleep Medicine scoring manual
 - Single epoch of phasic or tonic RWA =RWA
 - Chin EMG only
- Artifact in chin attributed to arousals, gross body movements, obstructive events
- ROC analysis to determine specificity for pediatric narcolepsy (NT1 and NT2)

Results

- **80% of children in our sample showed at least one epoch of RWA using AASM scoring criteria**
 - Likely reflects immature pontine-medullary inhibitory tracts
- **20% of NT1 and NT2 subjects had RBD**
 - No violent behaviors recorded; pantomime-like behaviors as reported in literature



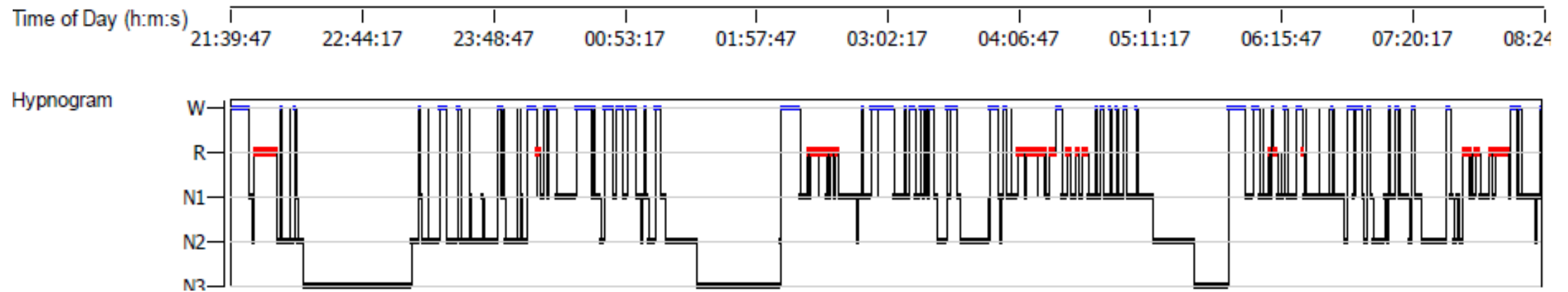
- Nocturnal RWA density is 15-30 x higher in children with narcolepsy than controls and IH patients respectively.
- Nocturnal RWA may be a biomarker to differentiate NT2 subgroup into more “NT1-like” or more “IH- like”

Nocturnal RWA Diagnostic Biomarker for Pediatric Narcolepsy (NT1 and NT2)

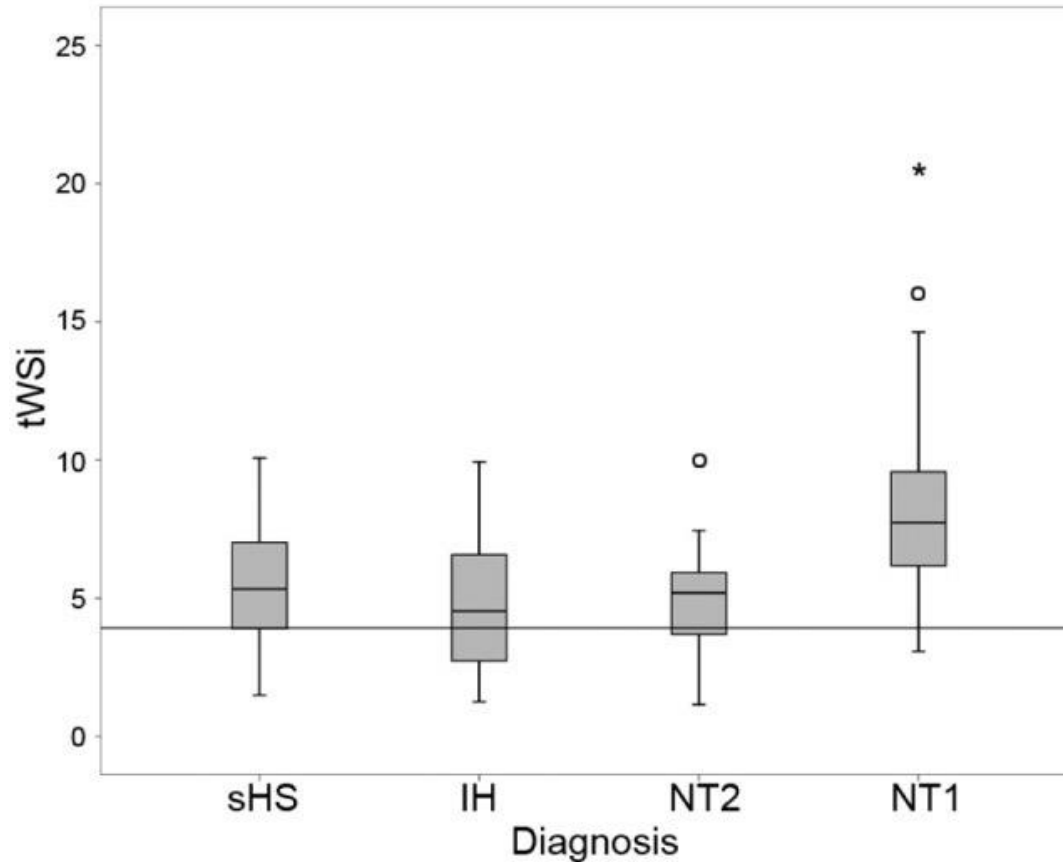
nRWA index AUC (95 CI)	0.87(0.75-0.99)	P<0.001
nRWA activity in ≥8% of REM epochs		
Sensitivity (%), 95 CI	52.9(27.8-77)	
Specificity (%), 95 CI	95.7(78.1-99.9)	
PPV (%), 95 CI	90 (55.7-98.5)	

Current Sleep Biomarkers for Narcolepsy Diagnosis: Sleep to Wake Transitions

- Hypocretin regulates sleep/wake state stability
- Low hypocretin results in disrupted nighttime sleep symptom
- Measured as increase in Wake-Sleep Transitions across the night



Sleep Wake Transitions



Wake-Sleep Transitions/Total Sleep Time

Overall group differences found

NT1 higher than other groups

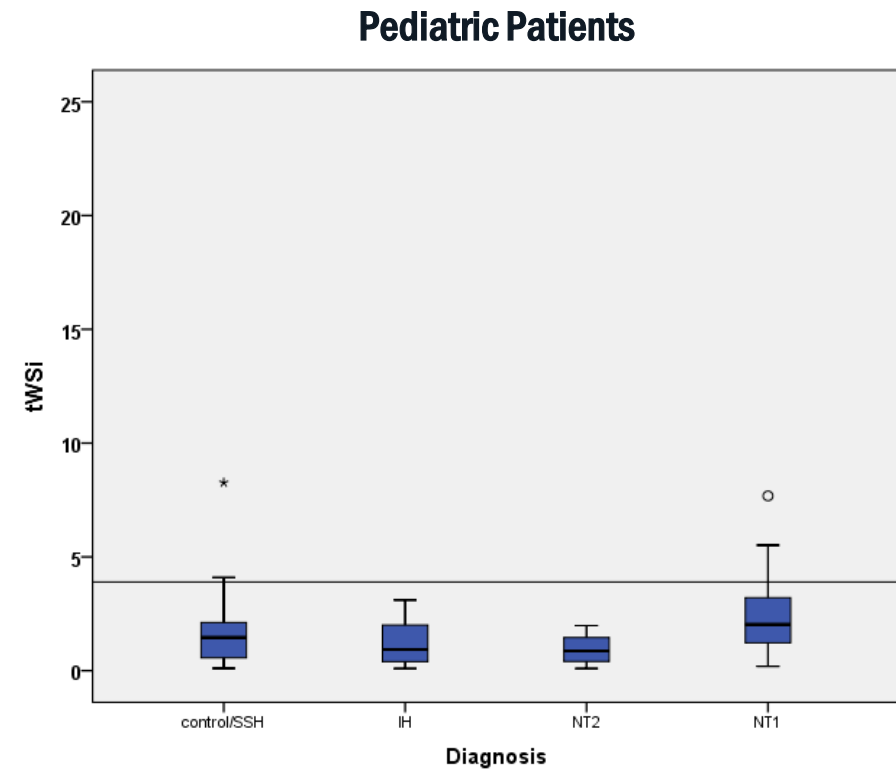
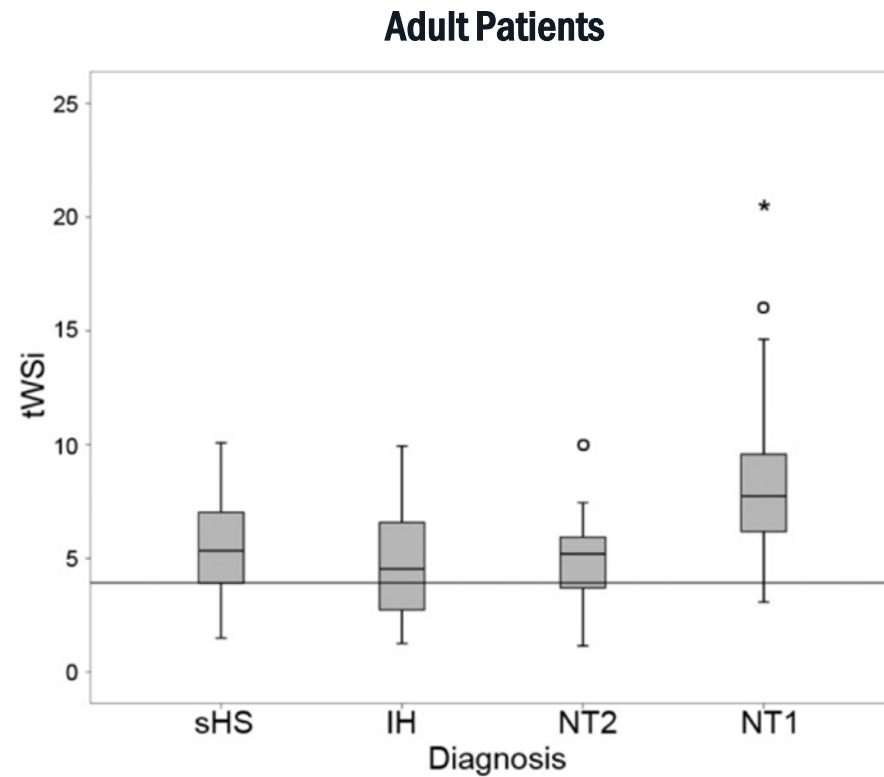
No differences between other groups

For NT1 dx:

Elevated Index >3.9/hour in bed was found in 96% of NT1 patients

Specificity only 31%...but in combination with SOREMP, could be promising diagnostic biomarker!

Children Have Fewer Sleep Wake-Transitions than Adult patients

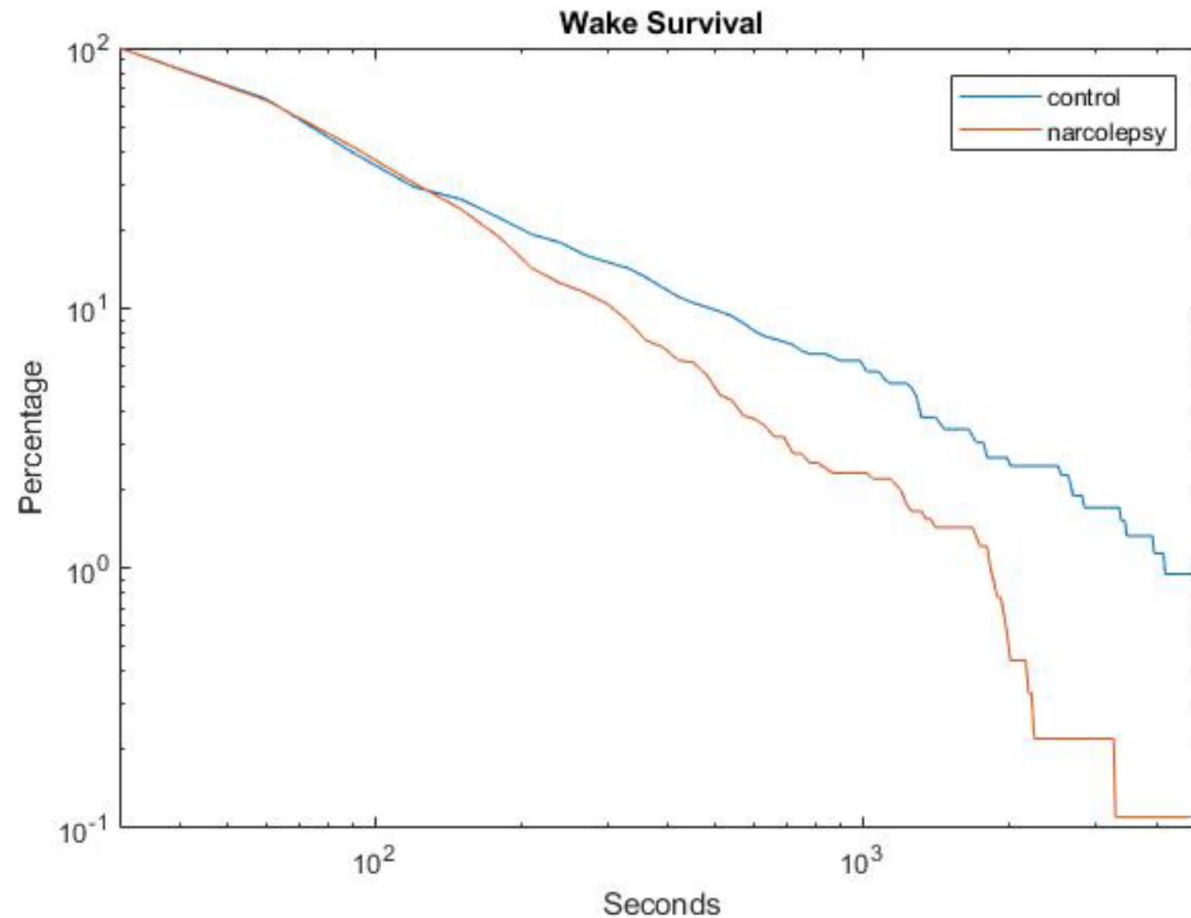


Sleep-Wake Transition Index is not a sensitive biomarker in children

Defining Disrupted Nighttime Sleep in Pediatric Narcolepsy

1. Is NREM sleep more stable in children and thus more resistant to sleep fragmentation in children with narcolepsy?
Or are wake periods shorter and thus less disruptive to sleep continuity?
2. How should we define and measure DNS in pediatric narcolepsy?
Variably defined in adult narcolepsy studies: NREM 2/3 transitions to N1/W and REM transitions to N1/W
3. Could this definition of DNS be a diagnostic biomarker?

Wake Bouts are Shorter in Pediatric NT1 Patients



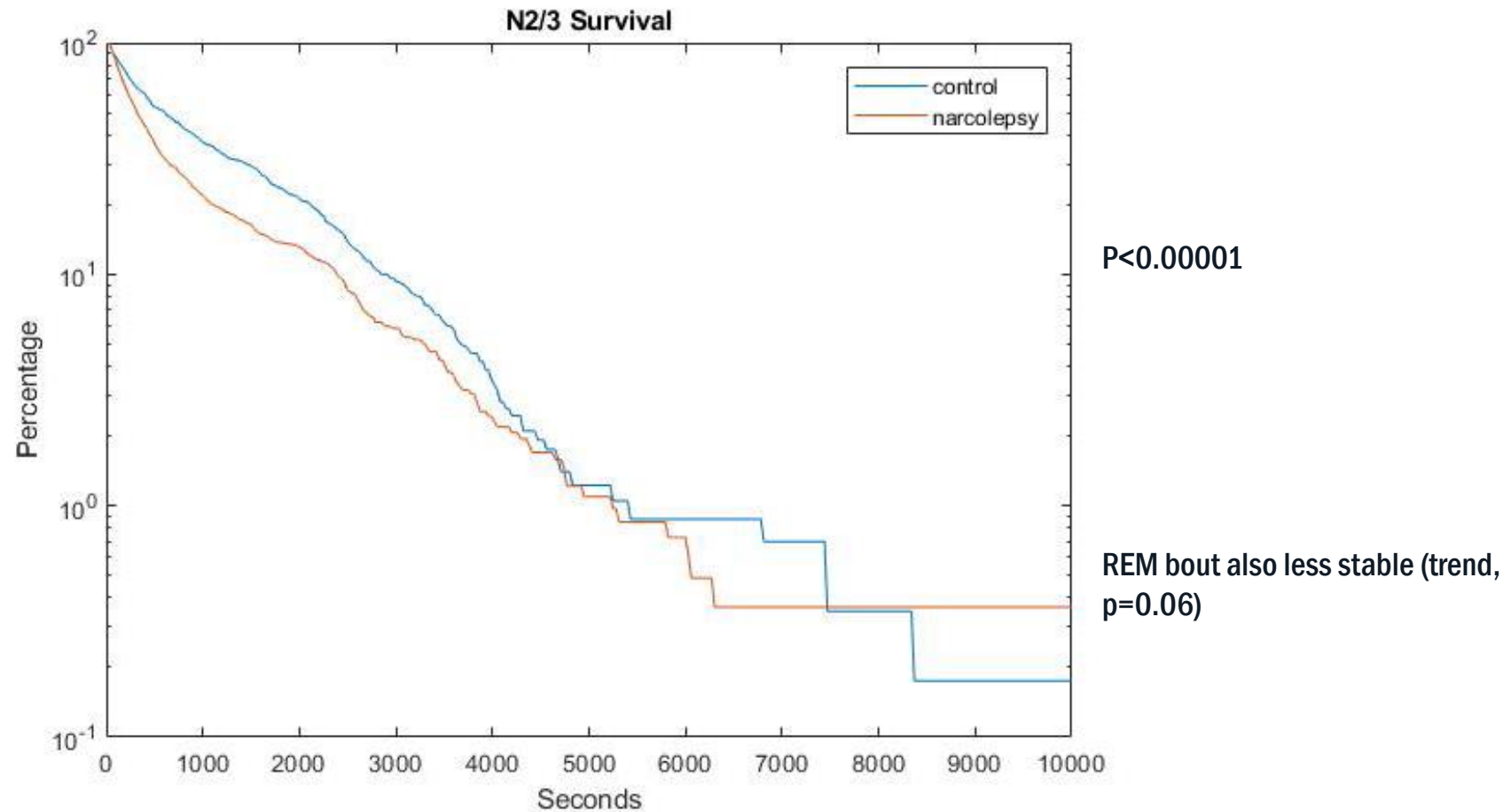
N=25 NT1
N=25 subjectively sleepy
controls

P=0.007

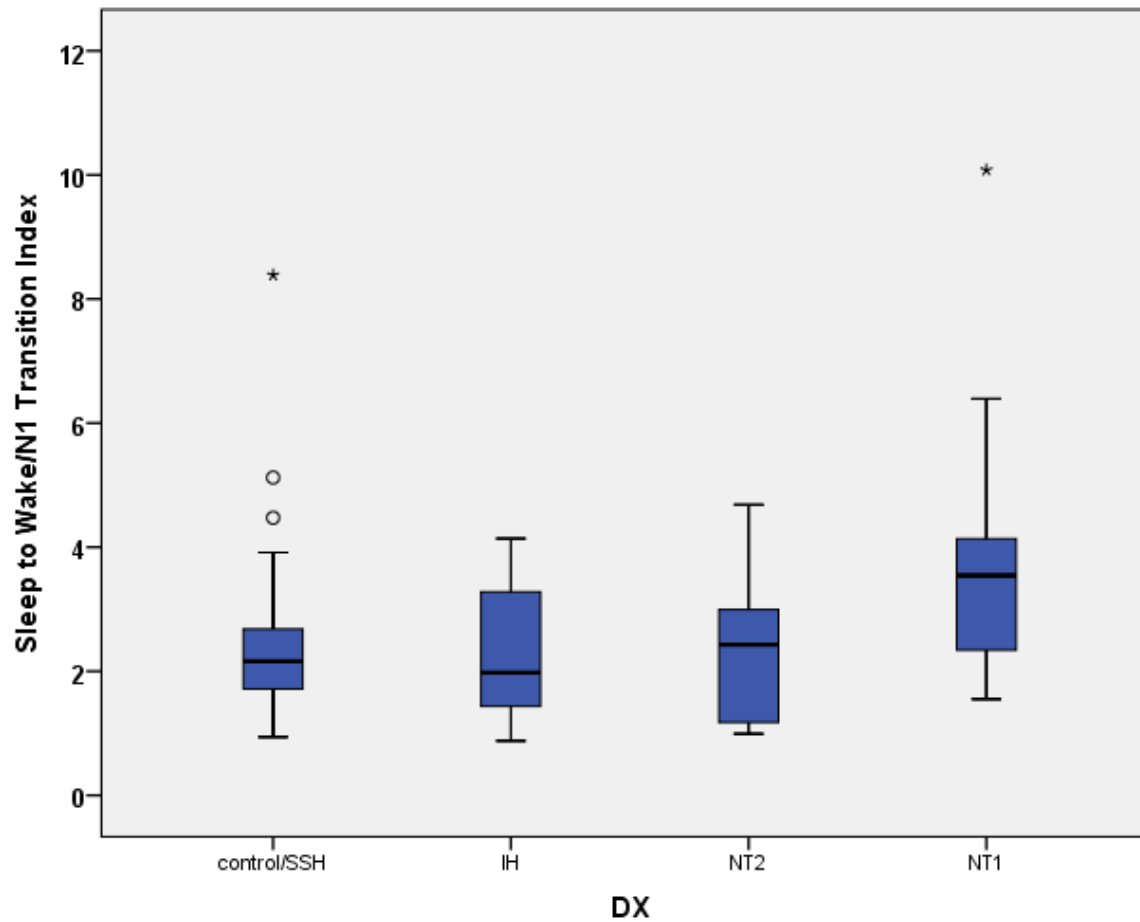
No difference in NREM
stage 1 bout durations

Majority of wakings in
children are brief
<2 minutes but
pediatric NT1 rarely
can sustain wake
periods >10 minutes

NREM stage 2/3 bouts are Not Stable in Pediatric NT1 patients



DNS As Defined as Sleep to Wake/N1 Transitions is Most Severe in NT1 Patients



DNS in Pediatric NT1 can be Defined as ...

- Short, frequent waking periods during the night
- Frequent transitions from NREM 2/3 to Wake/N1
- Frequent transitions from REM sleep to Wake/N1
- A transitional pattern of sleep that fragments stable NREM sleep bouts (and possibly REM sleep as well)

Diagnostic yield of DNS is less than nocturnal RWA (AUC 0.75 vs. 0.87)

Pediatric Biomarkers Summary

- Hypersomnia conditions commonly begin before age 18 years
- Diagnostic delays/misdiagnosis are common in this group
 - Health/psychological/safety consequences of these delays
- There are a number of clinically useful diagnostic sleep biomarkers for NT1 extractable from the nocturnal PSG that can improve diagnostic accuracy
- nSOREMP, Wake/N1 transitions in to REM, nocturnal RWA are very specific to NT1
 - NT2 patients have these biomarkers but results are more variable
 - May be useful in predicting prognosis “stable narcolepsy” or may symptoms may improve over time

Pediatric Biomarkers Summary

- **Disrupted Nighttime Sleep** can be defined across adult and pediatric narcolepsy patients
 - high number of transitions from NREM stage2/3 and REM sleep to NREM stage 1 or wake
 - **DNS** may not be as specific a biomarker as other REM abnormalities but clearly can distinguish NT1 from other hypersomnia disorders
 - **IH** in pediatric populations does not have the REM abnormalities or high sleep stage transitions of NT1 (and more variably found in NT2)
 - Could help with objective phenotyping patients to improve reliability of testing
- * Need for large data registries of PSGs/MSLTs to further refine sleep biomarkers unique to hypersomnia disorders

Coming Soon – Pediatric Hypersomnia Tool

You are being asked questions about symptoms of a possible sleep problem. Think about your last week while you were in school when choosing your answers.

Check "Often" if the symptom happens 3 times or more per week.
 Check "Sometimes" if the symptoms happens 1-3 times per week
 Check "Never" if you do not have the symptom
 Check "DNK" for do not know if you are not sure if you have the symptom,

	<u>Often</u> (≥ 3/week)	<u>Sometimes</u> (1-3/week)	<u>Never</u> (Never noted)	<u>DNK</u> (Do not know)
1 I fall asleep in class	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 I miss things in class because I am sleepy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 My friends tell me I fall asleep easily	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 I fall asleep in the bus/car after school	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5 I ask to go to the nurse's office or somewhere quiet to sleep during the school day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6 I feel weak in the knees when I laugh with my friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7 My voice slurs when I laugh hard	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8 My body feels weak briefly when I get excited or laugh	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9 I dream when I sleep at night	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10 My dreams seem very real	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11 When I wake up, I can't move for a few minutes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12 I write silly things when taking notes in class because I am sleepy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13 It takes me a long time to do my homework because I am so tired	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14 Doing homework makes me tired	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Aim: To identify children with hypersomnia conditions early and prompt referral to sleep disorder specialist for further evaluation

Goal: Validate and assess reliability in children being evaluated for hypersomnia conditions across the United States

Developed in collaboration with Wake Up Narcolepsy



Thank you!