Sleep as a Network State (Part I)

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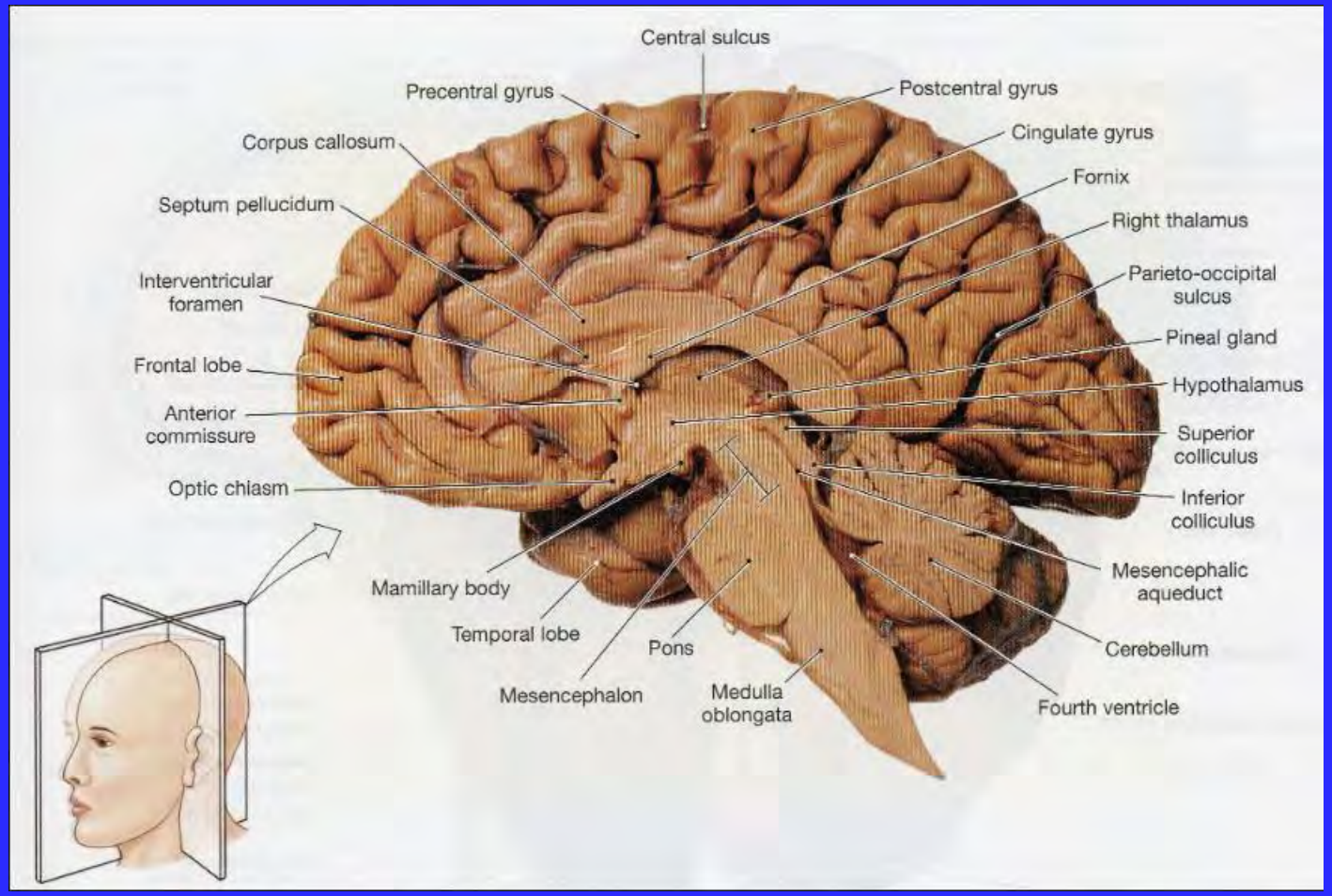
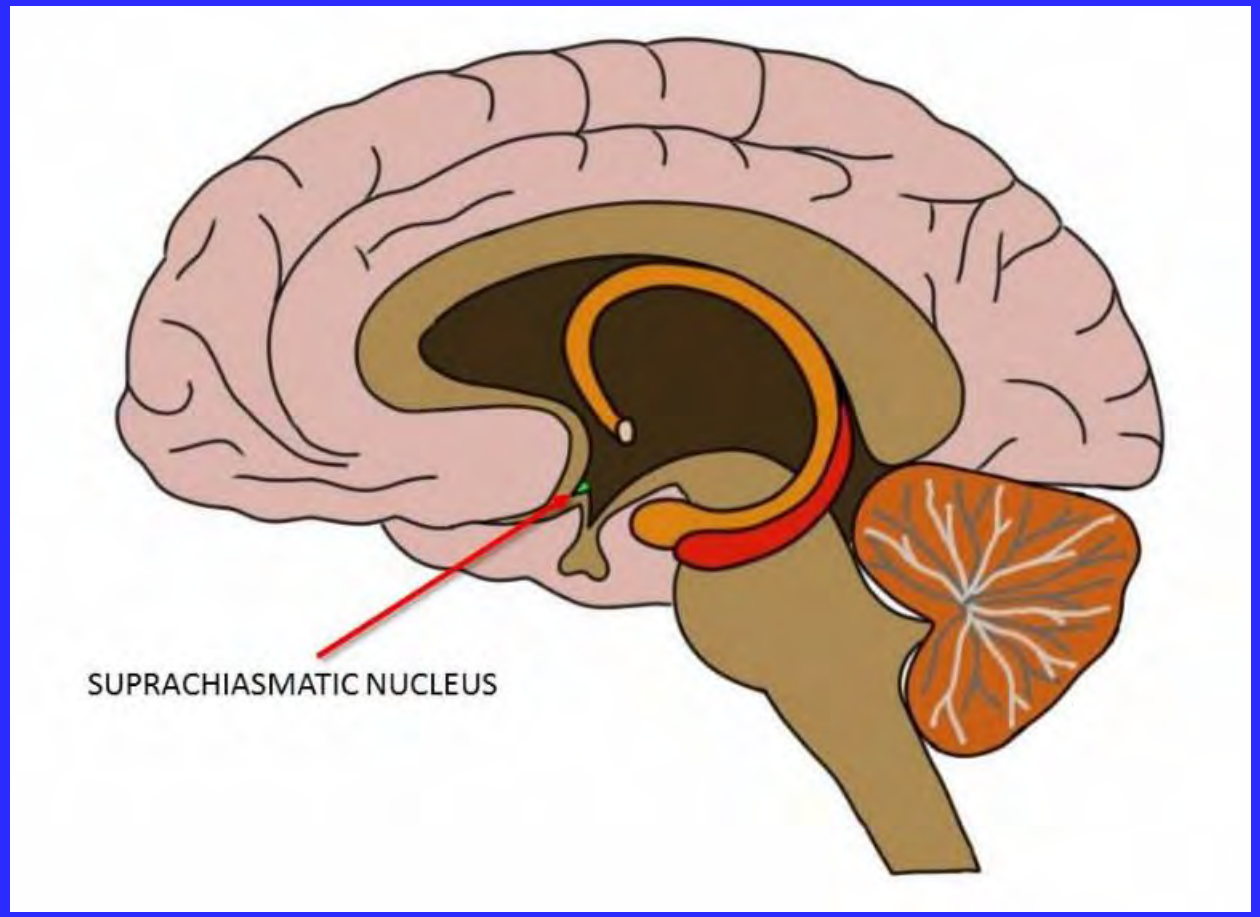
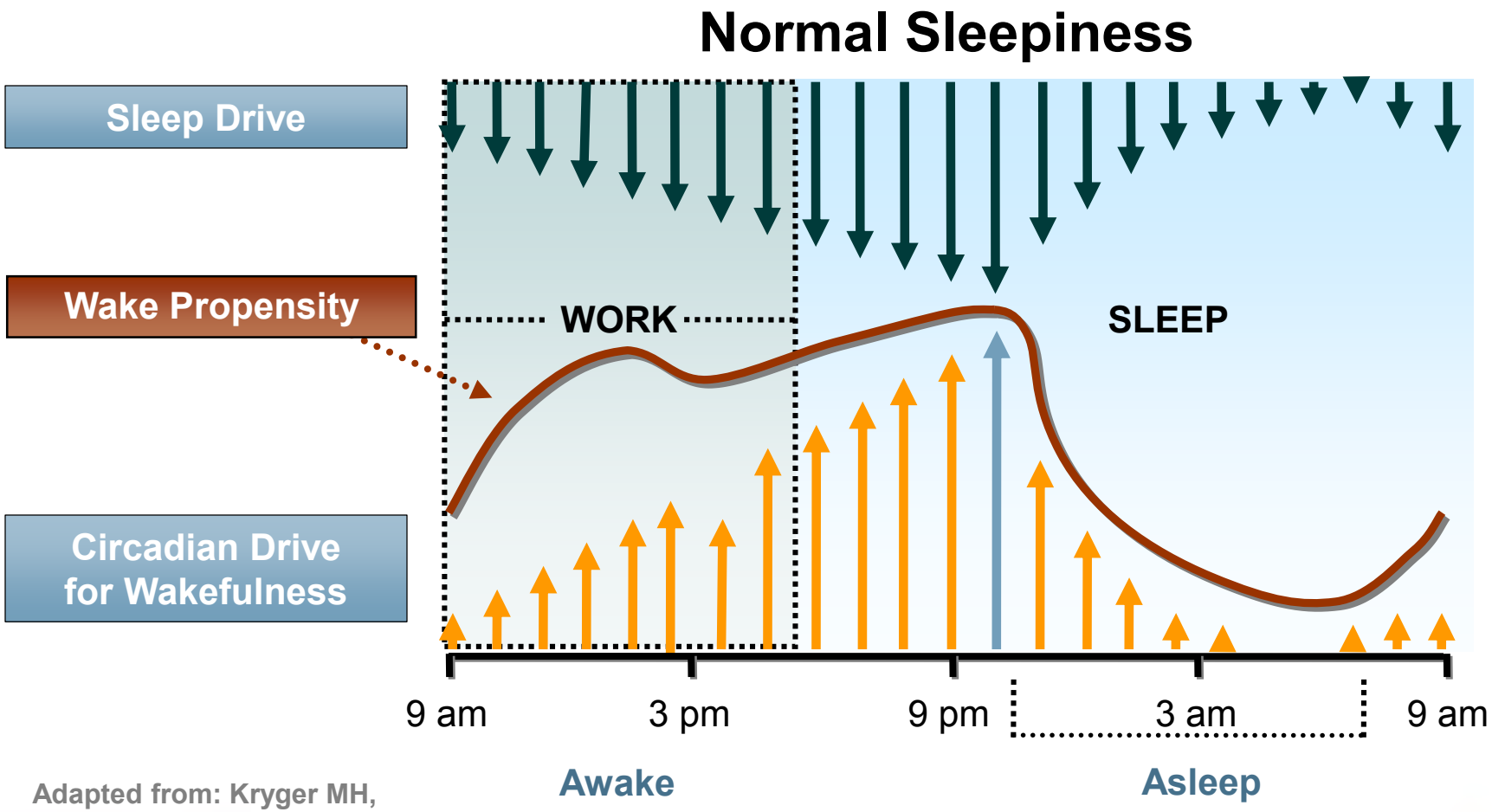
1. Thomas RJ, Mietus JE, Peng CK, Goldberger AL. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. Sleep. 2005;28:1151-61.


Central sulcus
Precentral gyrus
Postcentral gyrus
Corpus callosum
Cingulate gyrus
Septum pellucidum
Fornix
Right thalamus
Interventricular foramen
Parieto-occipital sulcus
Pineal gland
Frontal lobe
Hypothalamus
Anterior commissure
Superior colliculus
Optic chiasm
Inferior colliculus
Mamillary body
Mesencephalic aqueduct
Temporal lobe
Pons
Cerebellum
Mesencephalon
Medulla oblongata
Fourth ventricle


fineart
america


SUPRACHIASMATIC NUCLEUS

Physiologic Determinants of Sleepiness



Adapted from: Kryger MH, et al. Principles and Practices of Sleep Medicine. 2000.

Multi-system effects of sleep

Multi-system effects of sleep

- Brain “housekeeping”
  - Attention, executive function, memory, affective regulation
- Cardiovascular and autonomic resetting
- Metabolic regulation
  - Appetite regulation
- Inflammation control
  - Neuroendocrine and neuroimmune modulation
- Motor / musculoskeletal rest
  - Intuitive

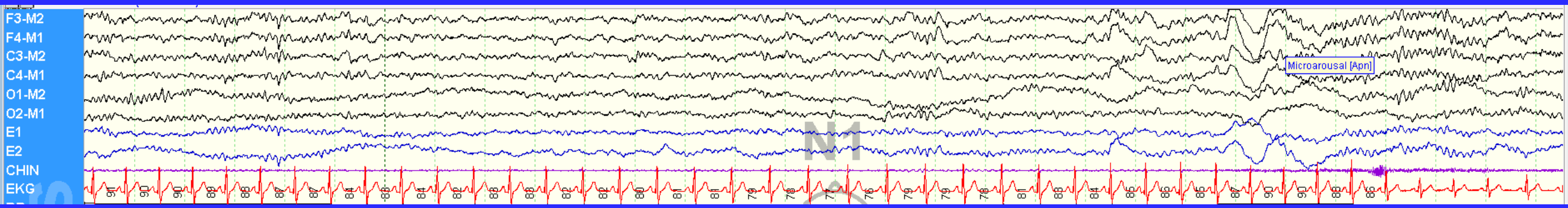
Cortical sleep

- Highly local process
  - Slow waves, UP/DOWN states, traveling waves
- Use-dependent features
- Complex network dynamics
  - Ocean waves
- Complex synaptic dynamics
  - Worm-like
  - Synaptic homeostasis model

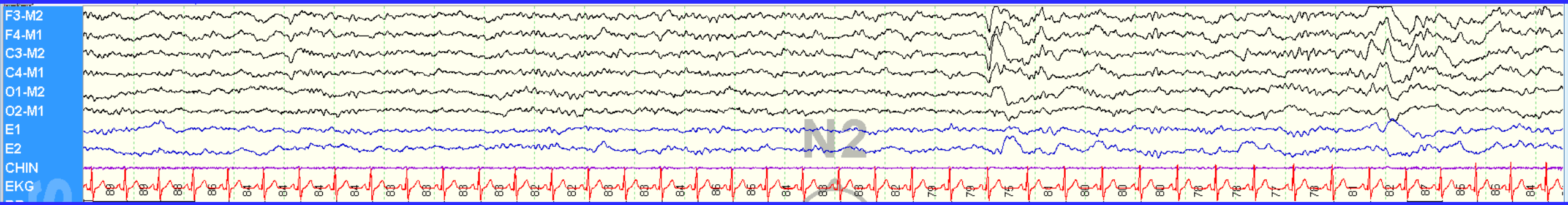
Measurement of sleep

- Classic EEG based
- Dense array EEG
- Respiratory
- Autonomic
- Movement
- Blood biomarkers
- Gene expression / transcriptome

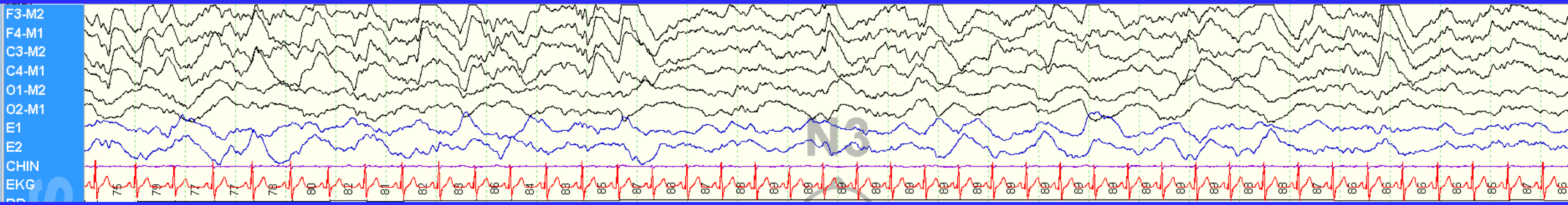
N1


F3-M2
F4-M1
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
EKG
Microarousal [Apn]
N1

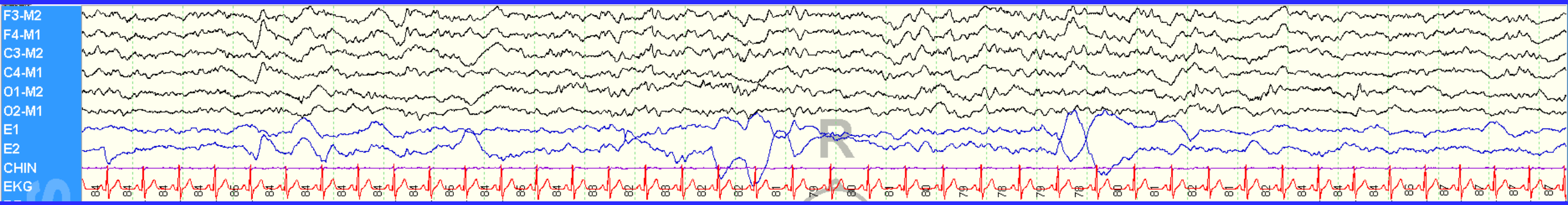
N2



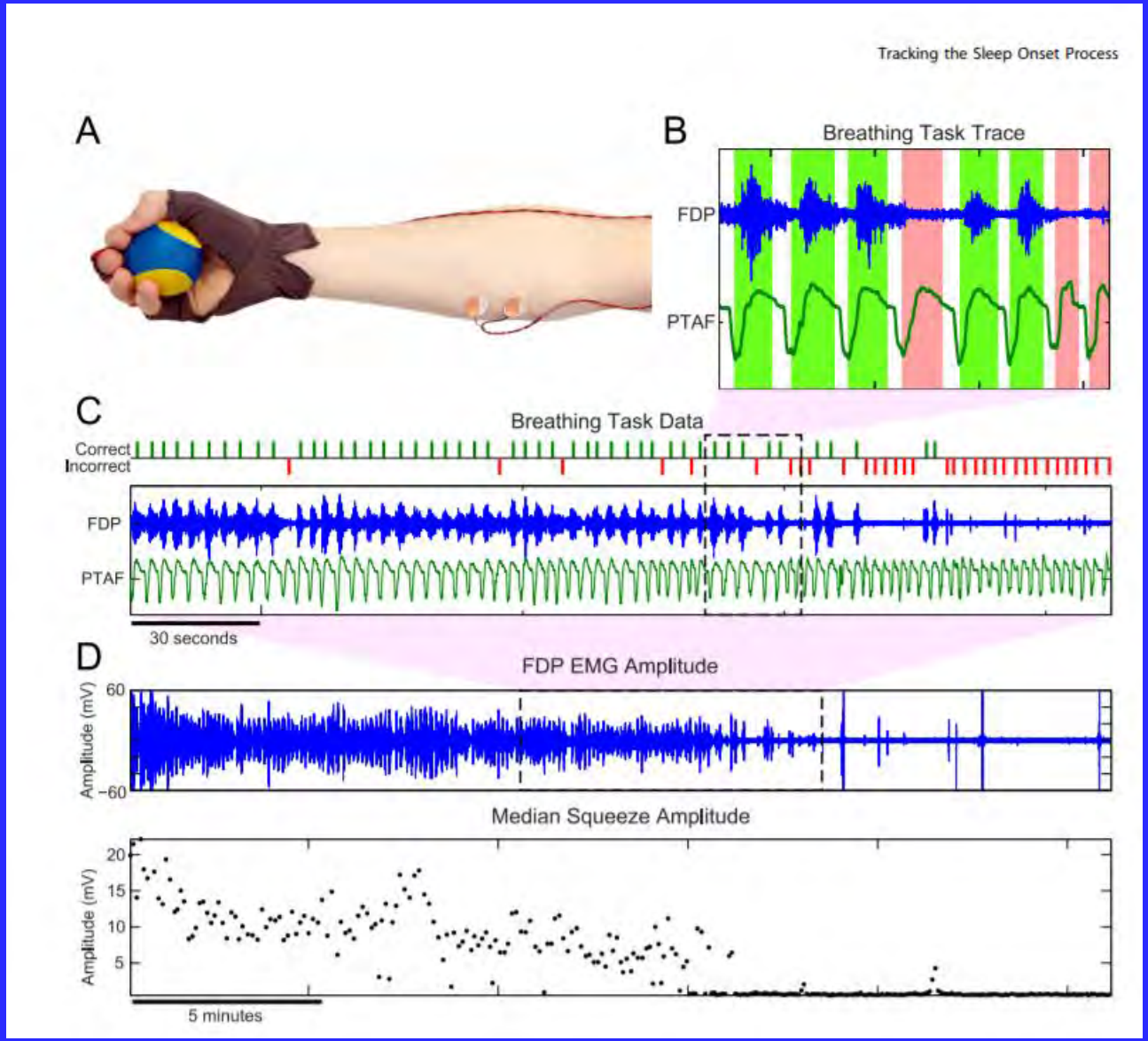
N3



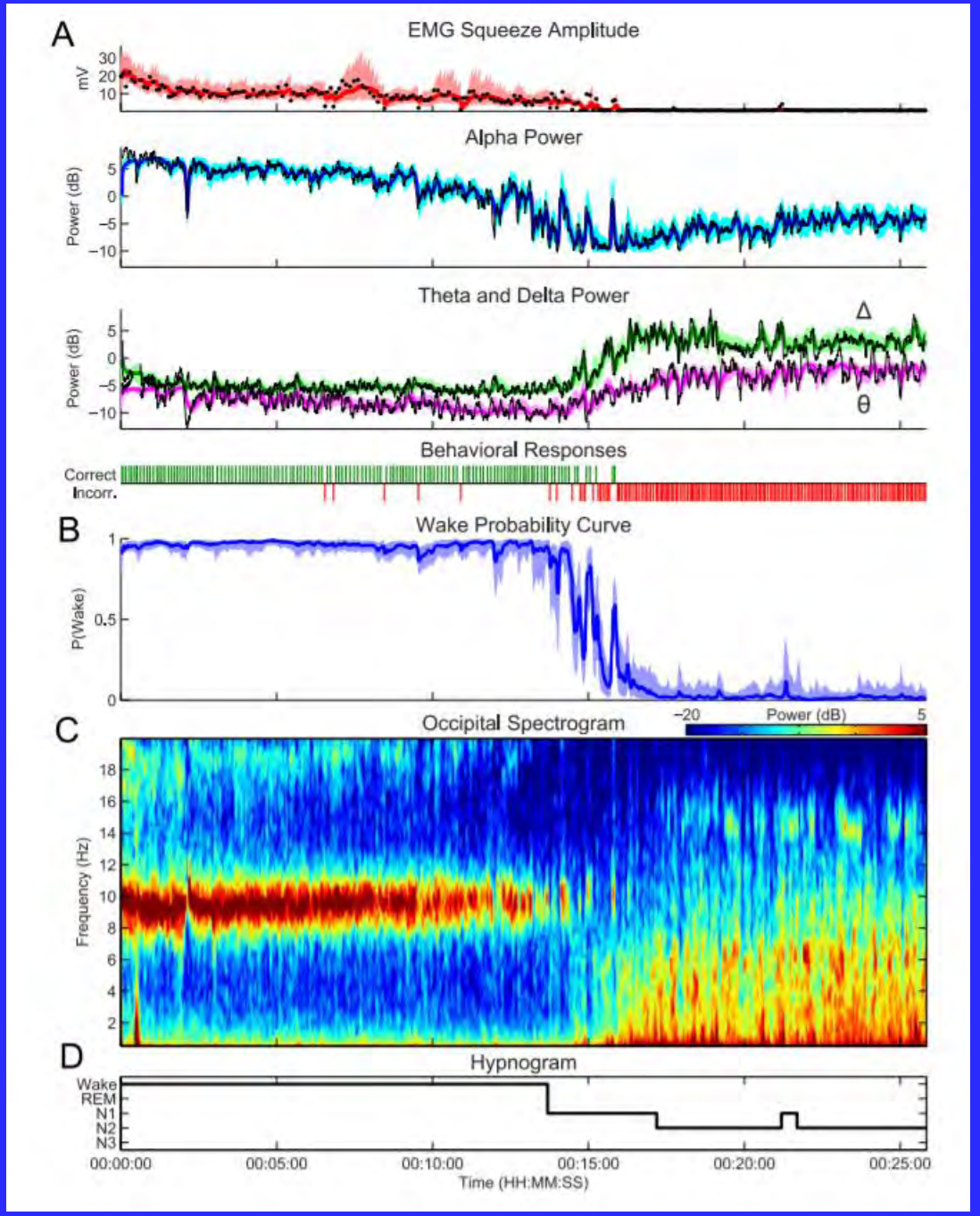
REM



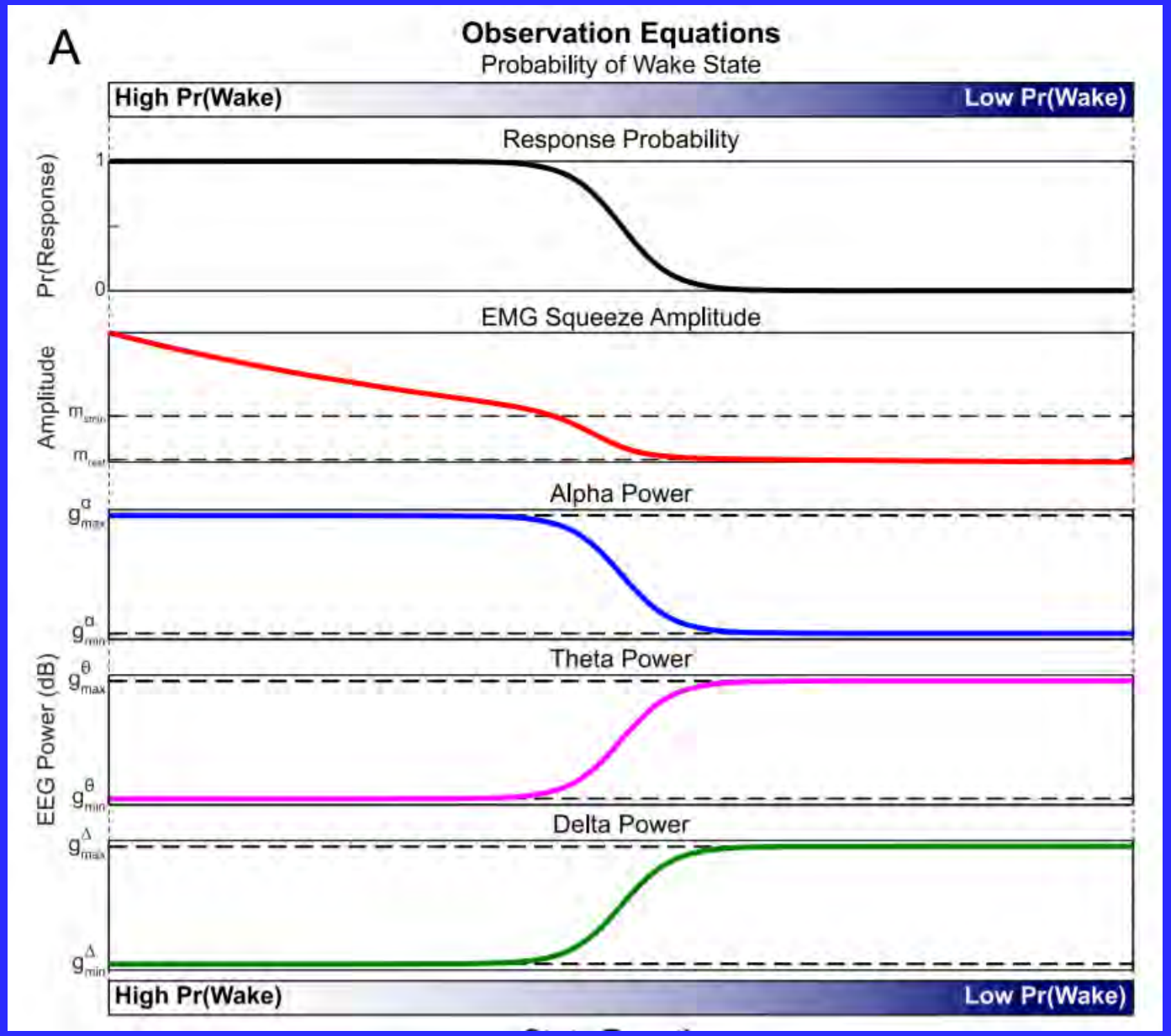
Sleep Onset


Tracking the Sleep Onset Process
A
B
Breathing Task Trace
FDP
PTAF
C
Breathing Task Data
Correct
Incorrect
FDP
PTAF
30 seconds
D
FDP EMG Amplitude
Amplitude (mV)
60
−60
Median Squeeze Amplitude
Amplitude (mV)
20
15
10
5
5 minutes

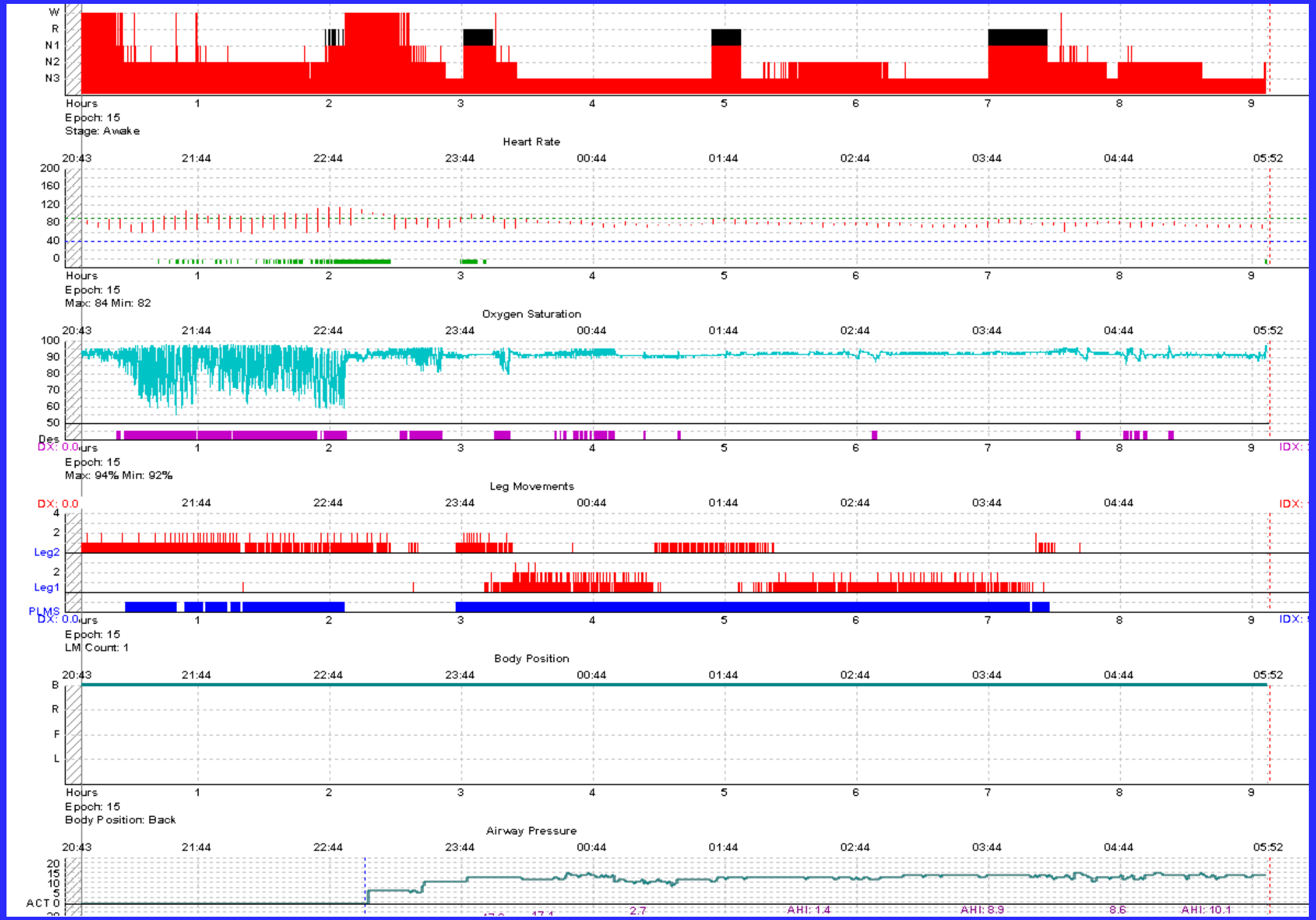
Sleep Onset


A
EMG Squeeze Amplitude
mV
30
20
10
Alpha Power
Power (dB)
5
0
−5
−10
Theta and Delta Power
Δ
θ
Behavioral Responses
Correct
Incorr.
B
Wake Probability Curve
P(Wake)
1
0.5
0
C
Occipital Spectrogram
−20
Power (dB)
5
Frequency (Hz)
18
16
14
12
10
8
6
4
2
D
Hypnogram
Wake
REM
N1
N2
N3
00:00:00
00:05:00
00:10:00
00:15:00
00:20:00
00:25:00
Time (HH:MM:SS)

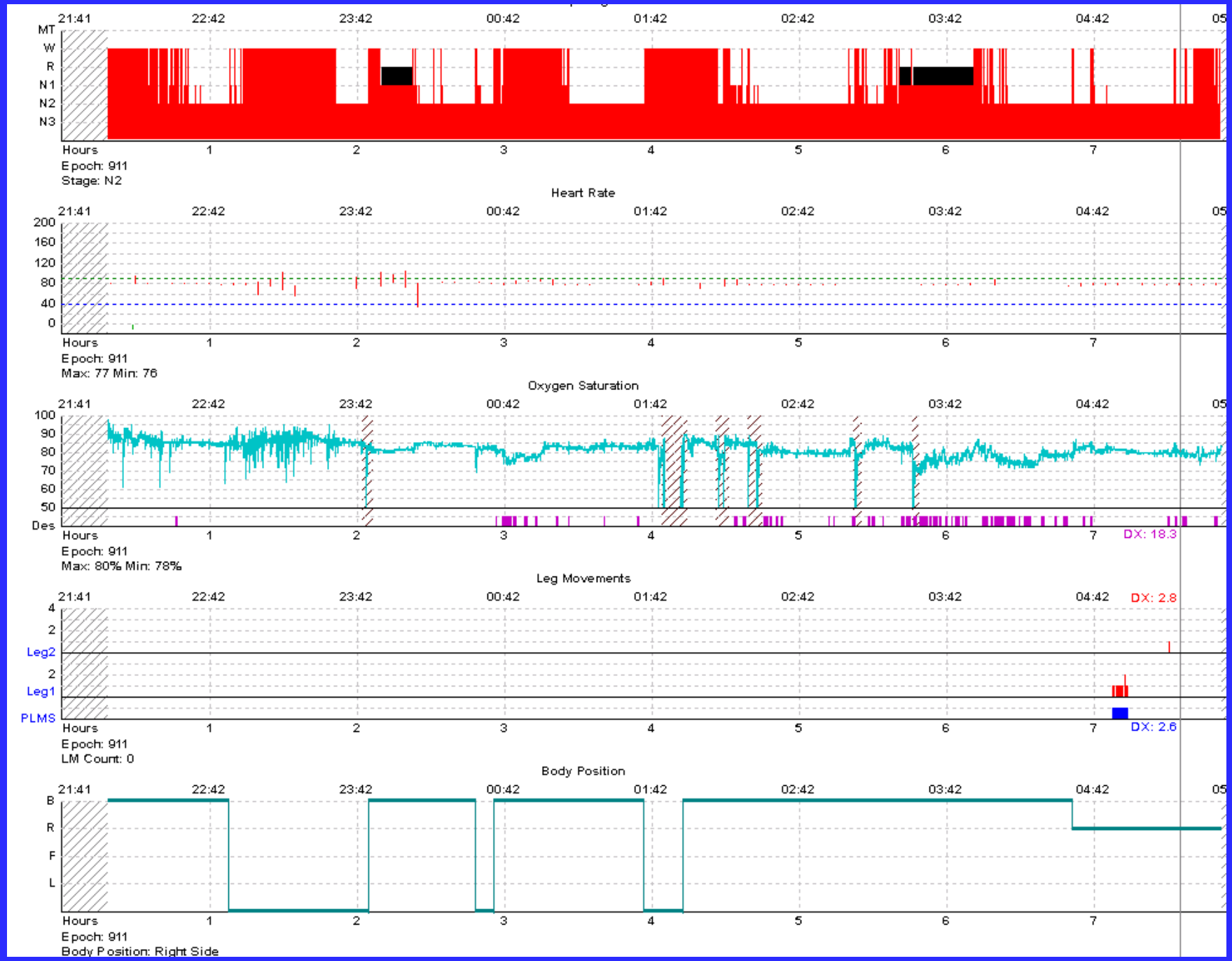
Sleep Onset


A
Observation Equations
Probability of Wake State
High Pr(Wake)
Low Pr(Wake)
Response Probability
Pr(Response)
1
0
EMG Squeeze Amplitude
Amplitude
Alpha Power
Theta Power
Delta Power
EEG Power (dB)
High Pr(Wake)
Low Pr(Wake)

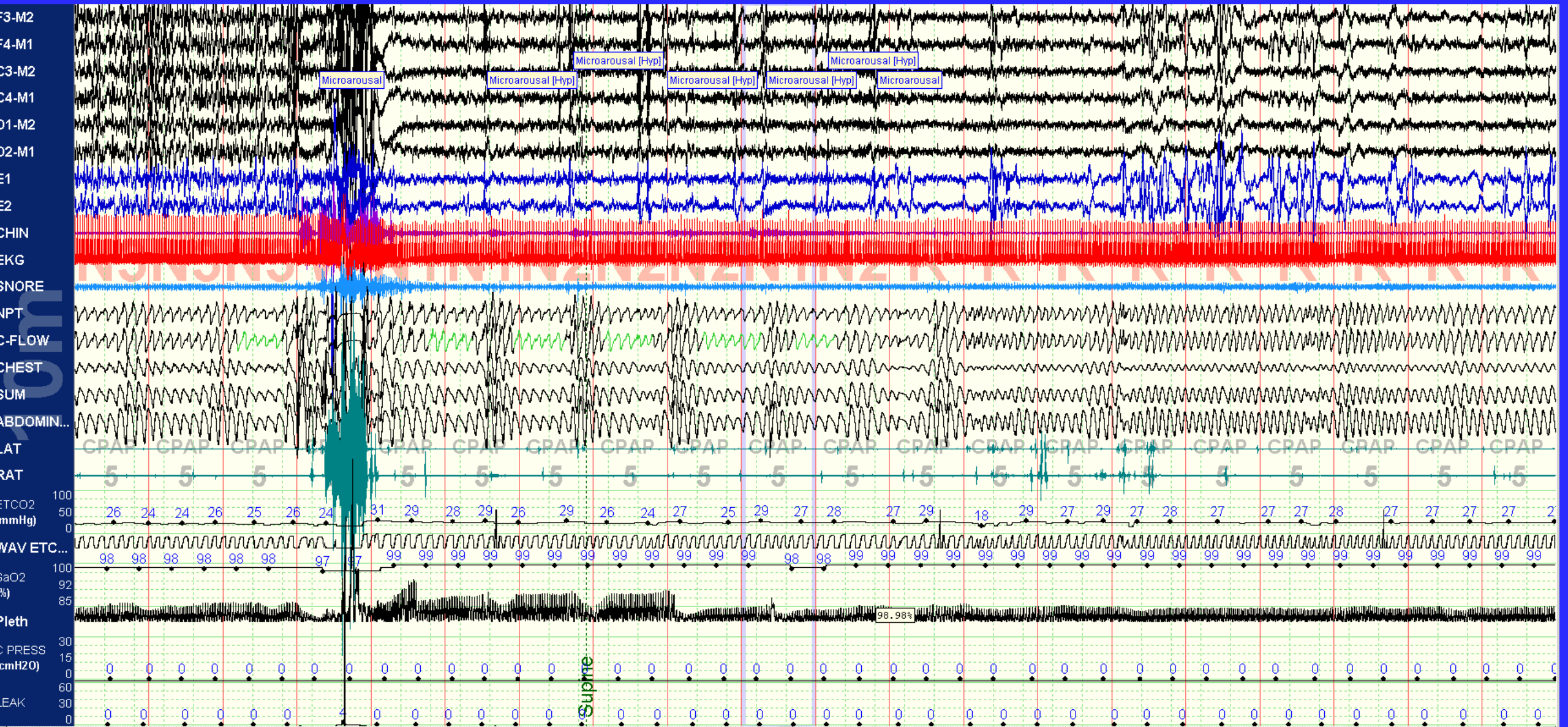
Classic Split Night



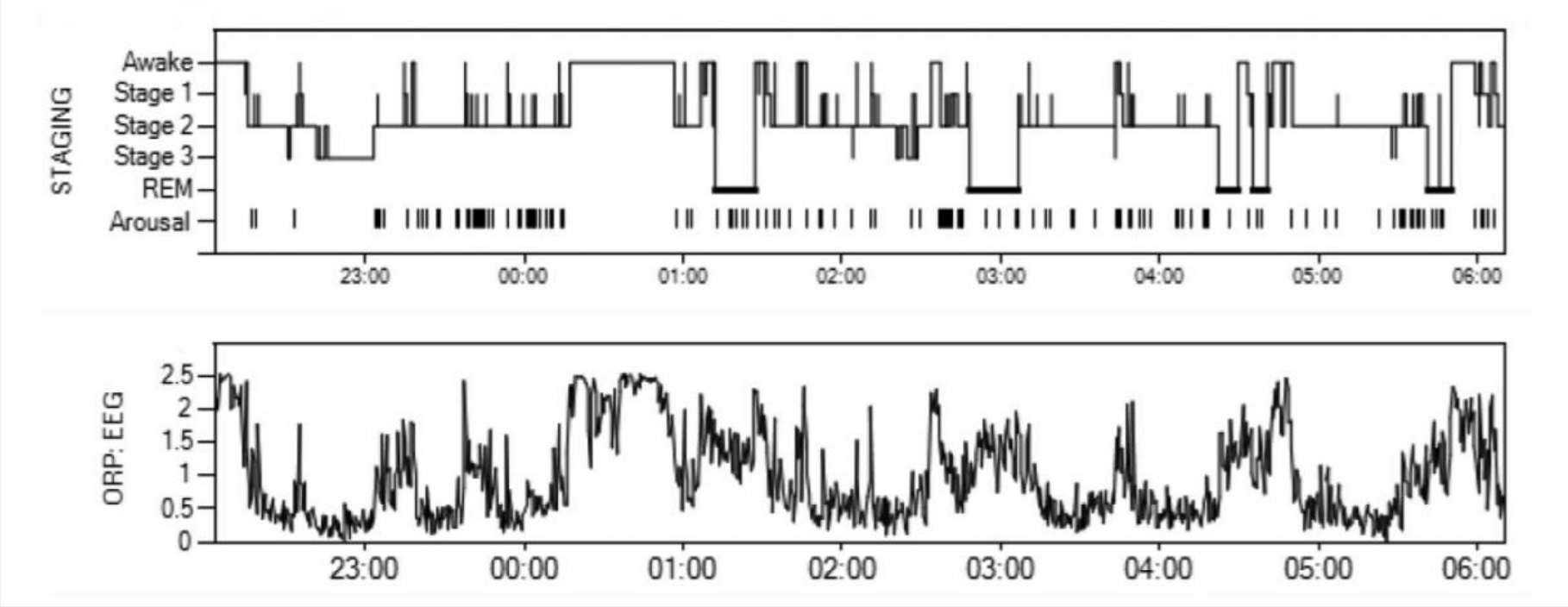
Macro-frag


21:41
22:42
23:42
00:42
01:42
02:42
03:42
04:42
MT
W
R
N1
N2
N3
Hours
Epoch: 911
Stage: N2
Heart Rate
200
160
120
80
40
0
Epoch: 911
Max: 77 Min: 76
Oxygen Saturation
100
90
80
70
60
50
Des
DX: 18.3
Max: 80% Min: 78%
Leg Movements
DX: 2.8
Leg2
Leg1
PLMS
DX: 2.6
LM Count: 0
Body Position
B
R
F
L
Body Position: Right Side

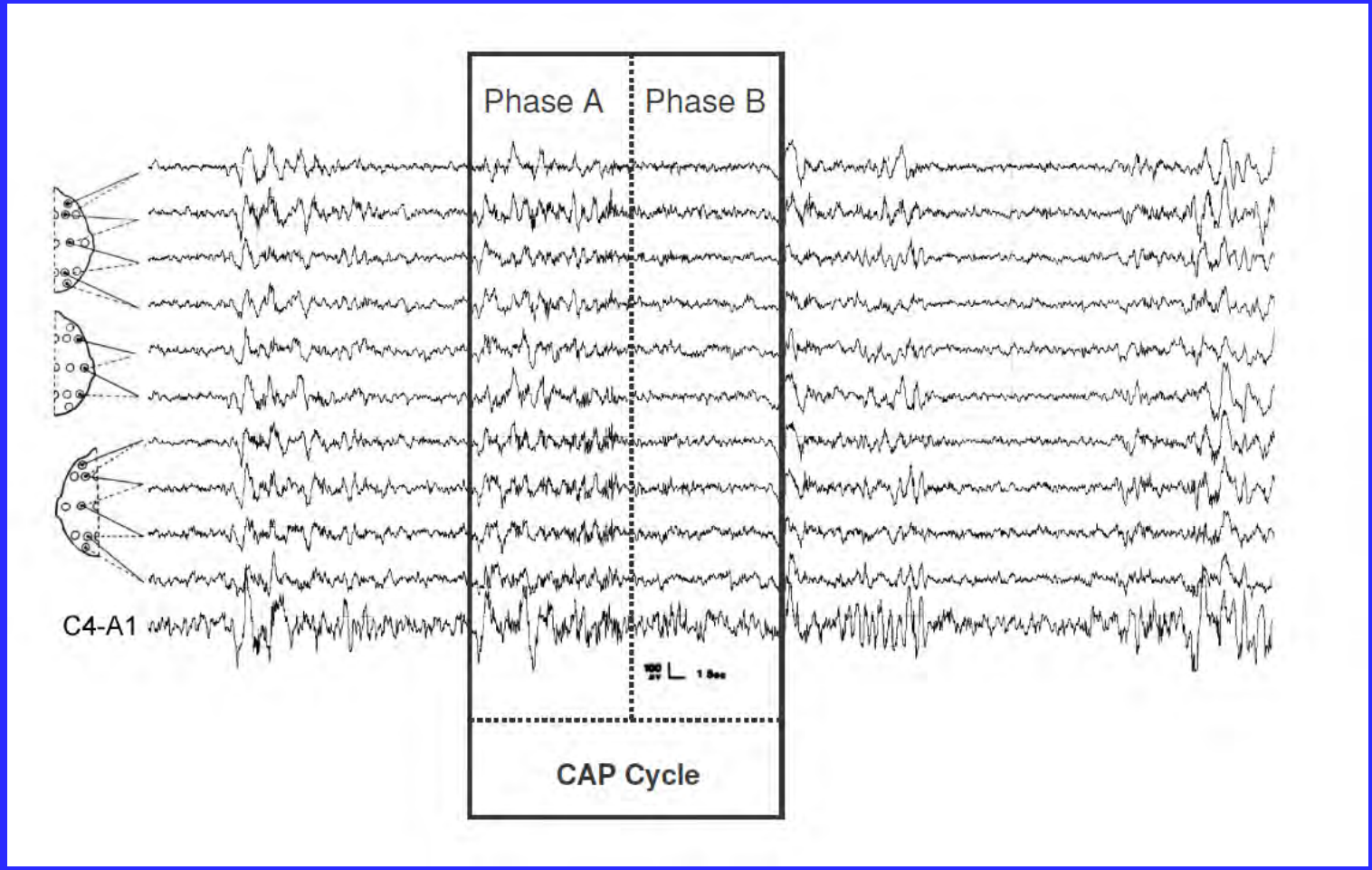
Classic Polysomnogram



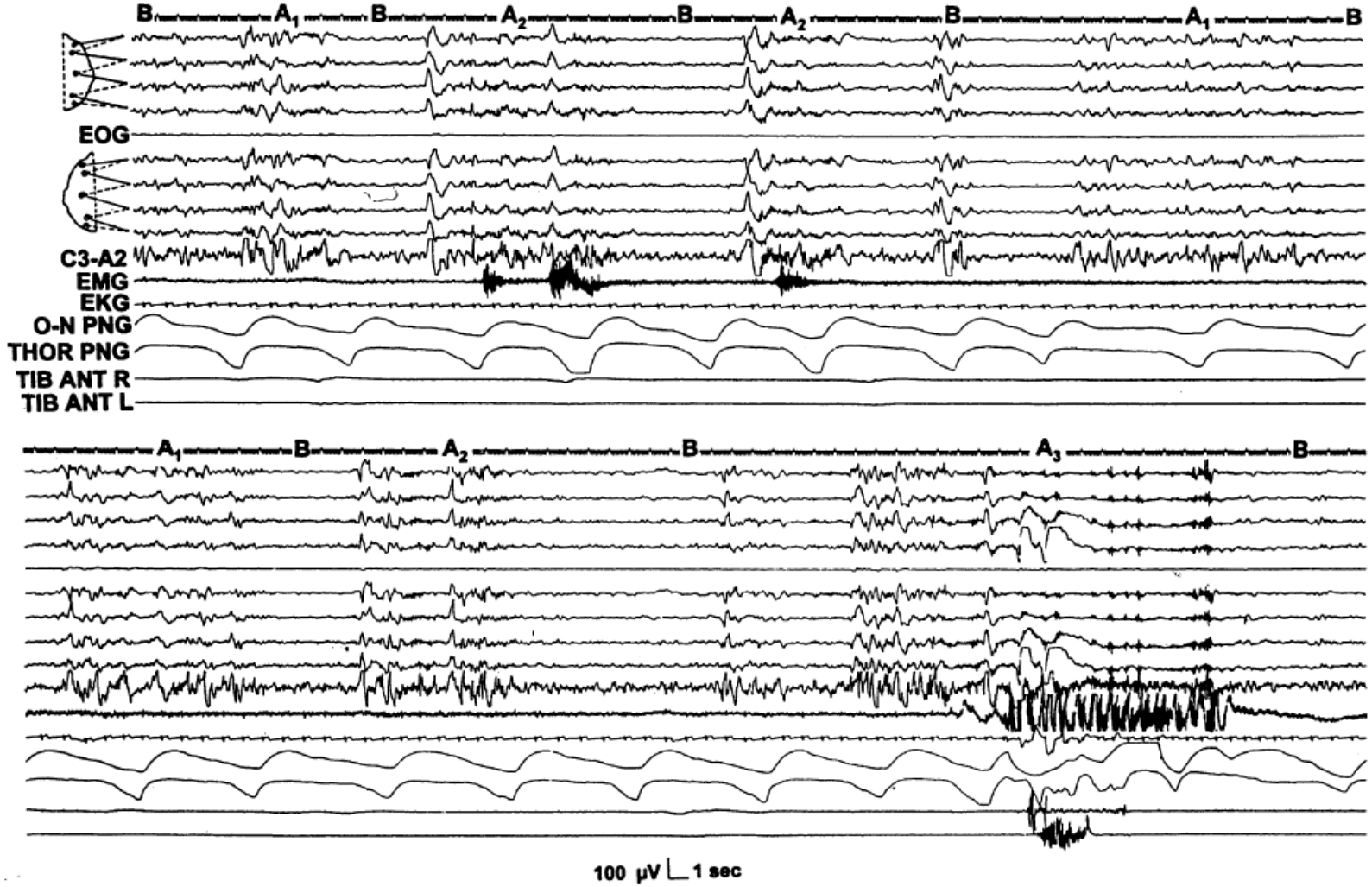
Standard signal, novel analysis (ORP)



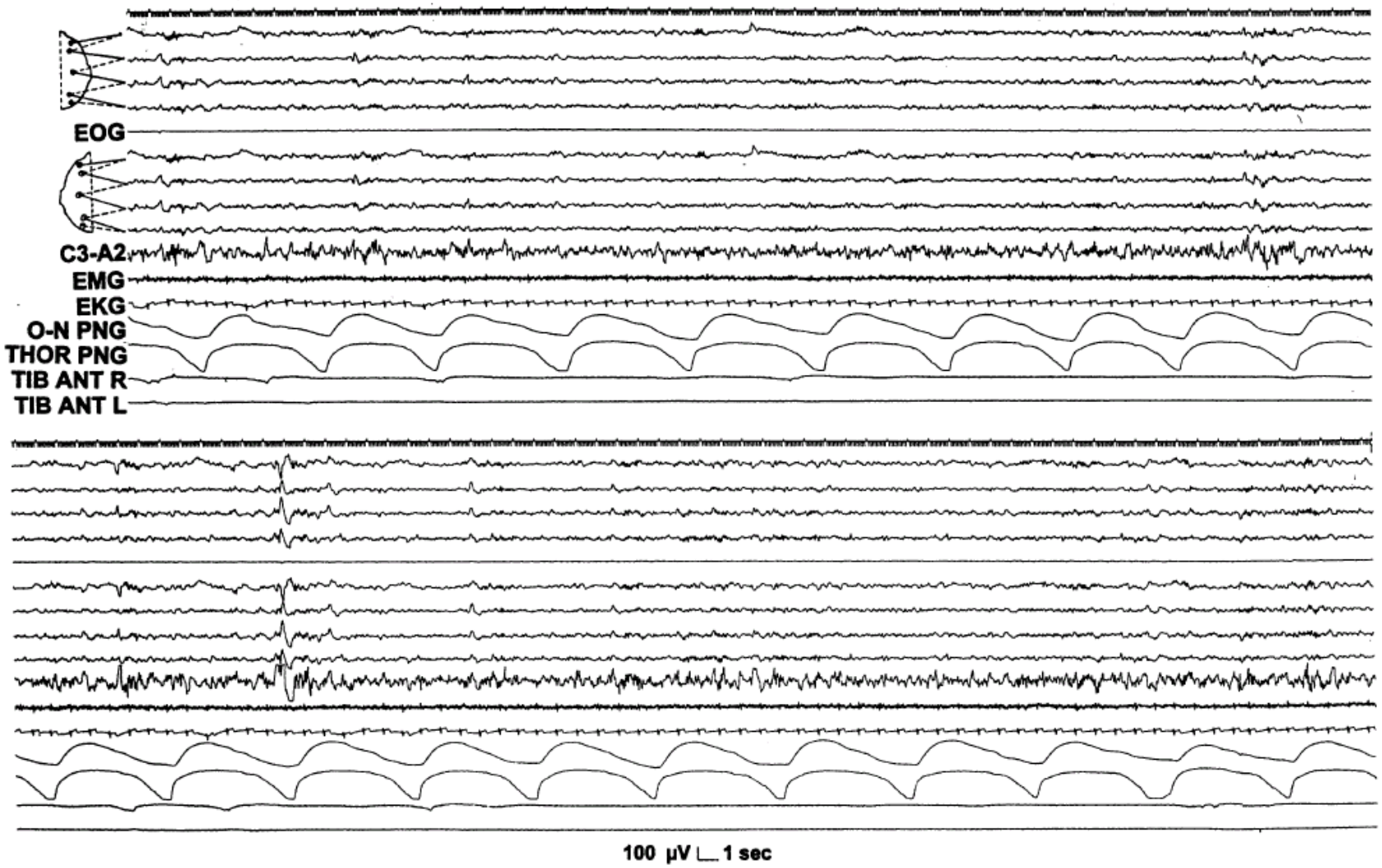
Cyclic Alternating Pattern (CAP)



A period of CAP which can go on for tens of minutes, markedly amplified in disease

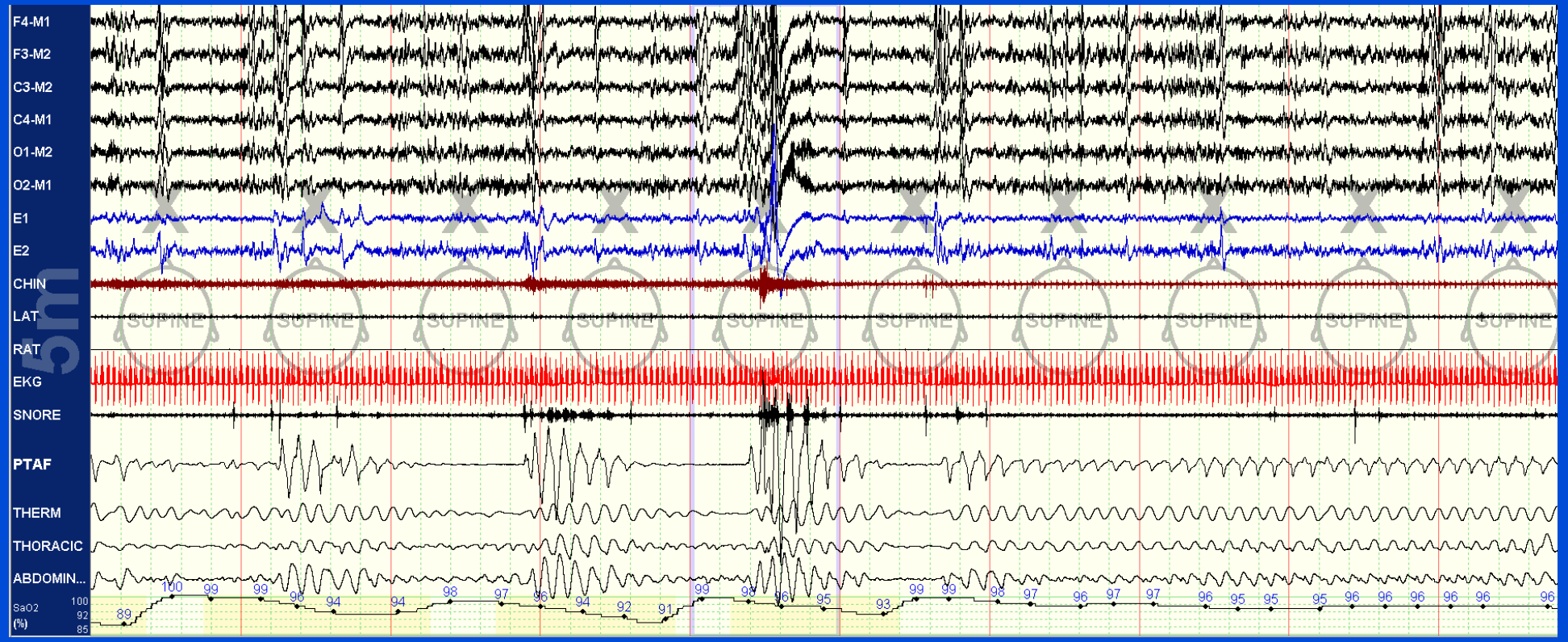


A period of EEG quiescence, which can go on for tens of minutes

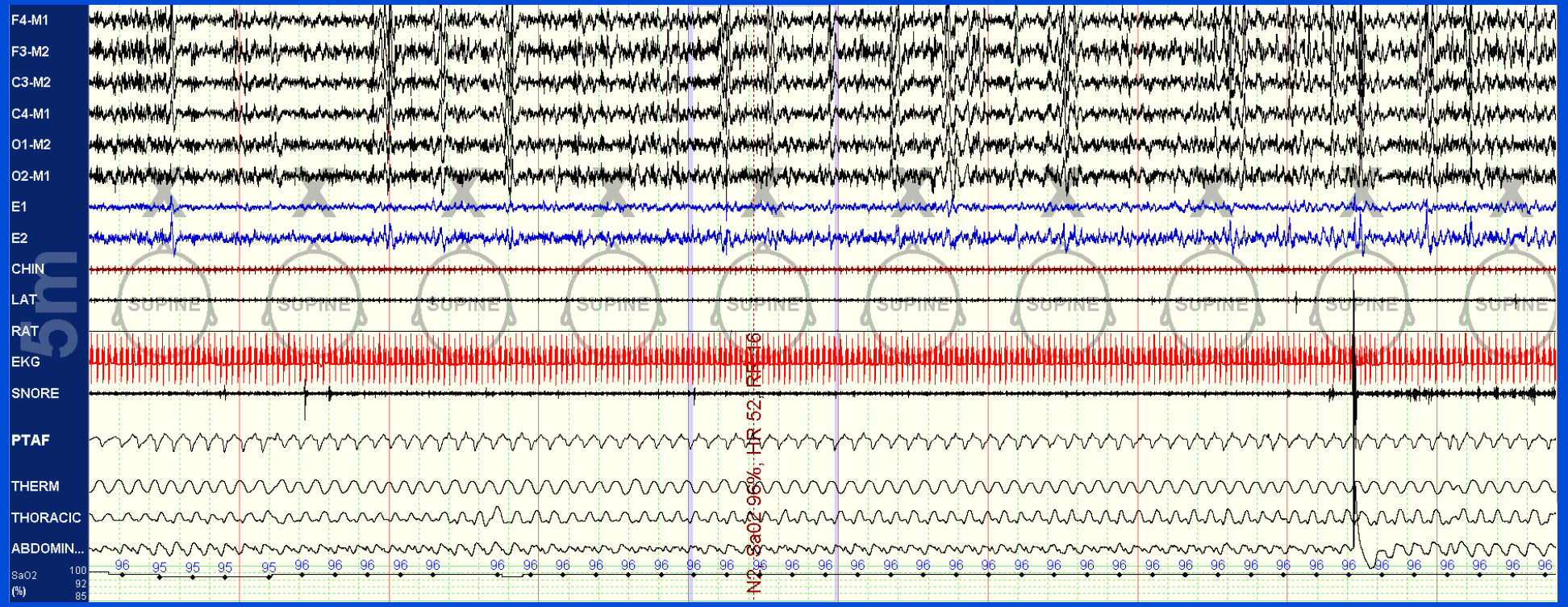


Unstable NREM

Transition to Unstable



Stable NREM


F4-M1
F3-M2
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
LAT
RAT
EKG
SNORE
PTAF
THERM
THORACIC
ABDOMIN...
SaO2 (%)
100
92
85
SUPINE
N2 SaO2 96%, HR 52, RR 16

Motivation

- Time to “RIP” the “gold standard” scoring guidelines?
- Scoring is biologically obsolete (if obsolescence is the gap between what is known and what is done)
- A network approach is one of several parallel methods which could be usefully implemented to enhance sophistication of sleep medicine and sleep science
- We see “network” but do not “think network” –
  - Tidal volume increases with arousals
  - Blood pressure surge with PLMs
  - Blood pressure non-sipping in insomnia
  - Large scale multi-physiology synchronized transients in sleep apnea

Overview

- Introductory concepts, sleep networks, breakdown syndromes
- < 1 Hz slow oscillation
- Thalamocortical networks
- Central autonomic network
- Cyclic alternating pattern and related concepts
- Stabilizing networks to target sleep disorders

Sleep is a unique network state

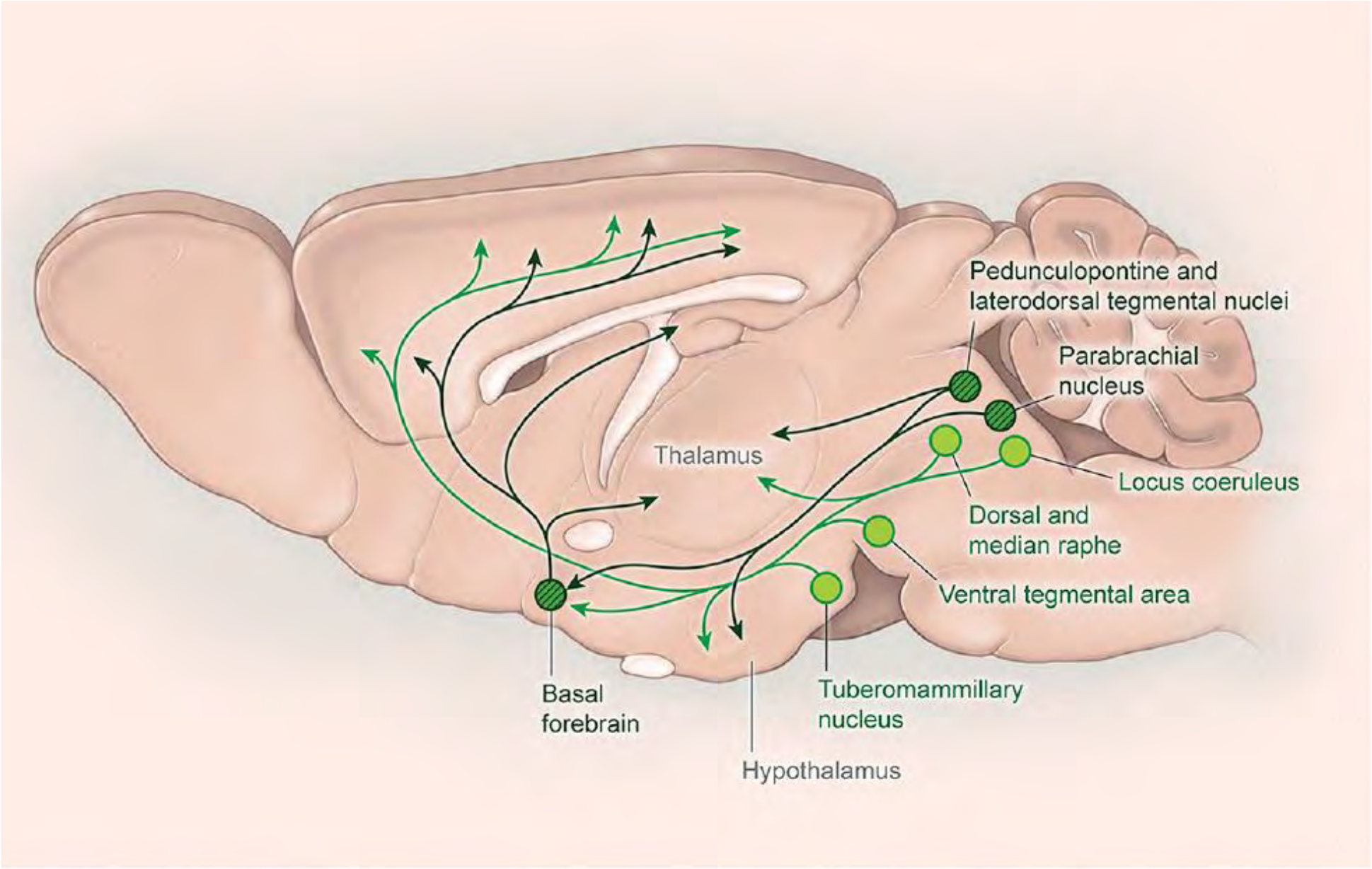
- Vastly disparate networks with vastly disparate functions
- Network activity may be intrinsic to a subsystem, integrated, or communicative (e.g., slow oscillation, spindles, long range integration from cortex to brainstem)
- Minimal overlap of fundamental oscillatory outputs
  - Spindles, heart rate, slow oscillation, cyclic alternating pattern
- Components dispersed in space
- Necessity to travel in time
- Individual sleep sub-systems have different driving mechanisms
  - Sleep homeostatic drive for slow wave power
  - Hypoxia or hypercarbia for respiration

Sleep Networks

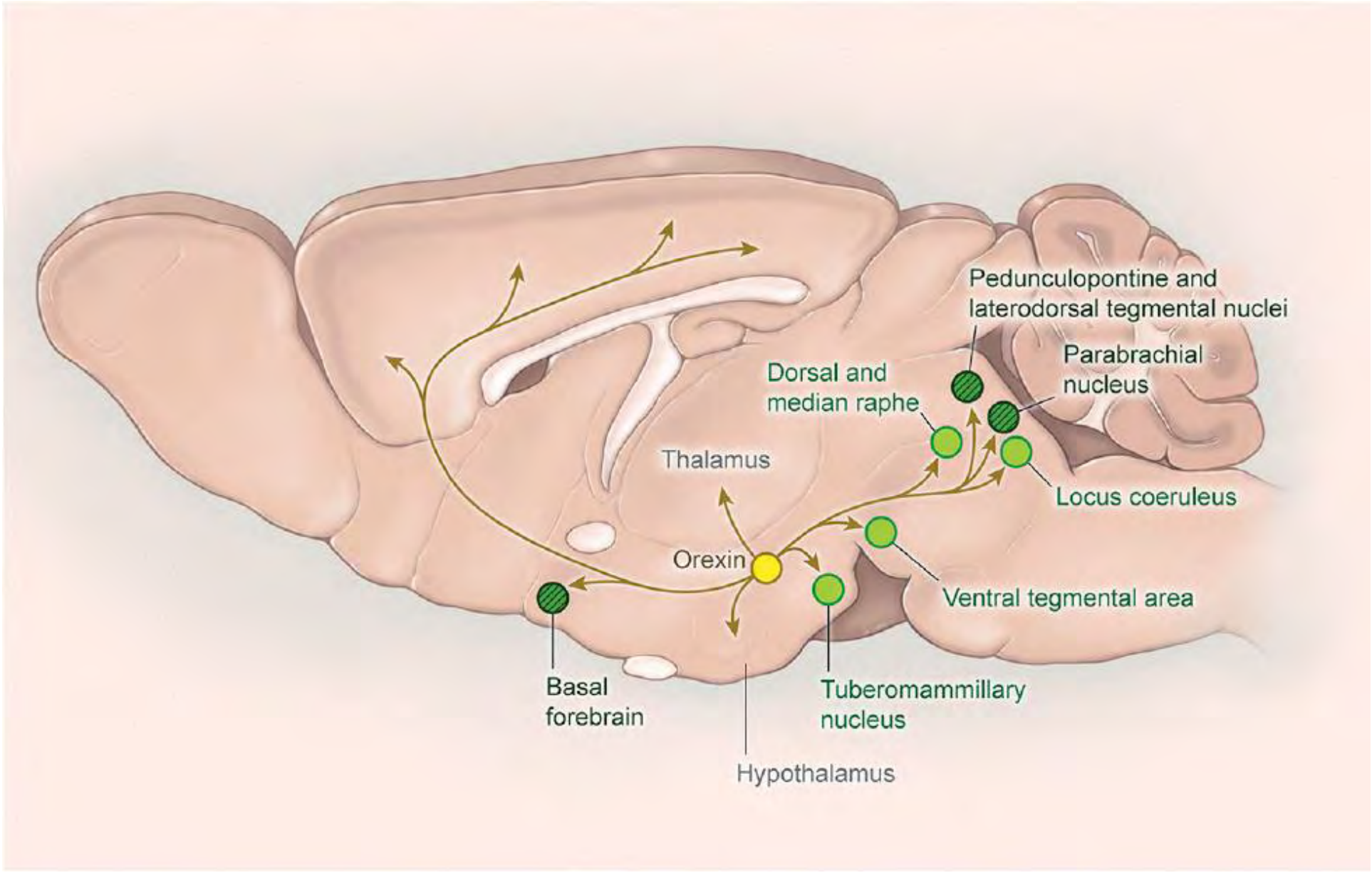
- Cortical
- Thalamocortical
- Intra-thalamic
- Brainstem
- Chemoreflex
- Baroreflex
- Central autonomic network
- REM-NREM
- Wake to sleep transition
- Arousal
- Respiratory generative
- Respiratory control
  - Rhythm
  - Airway
- Motor control
  - Periodic
  - Aperiodic
- Cardio-autonomic

Wake

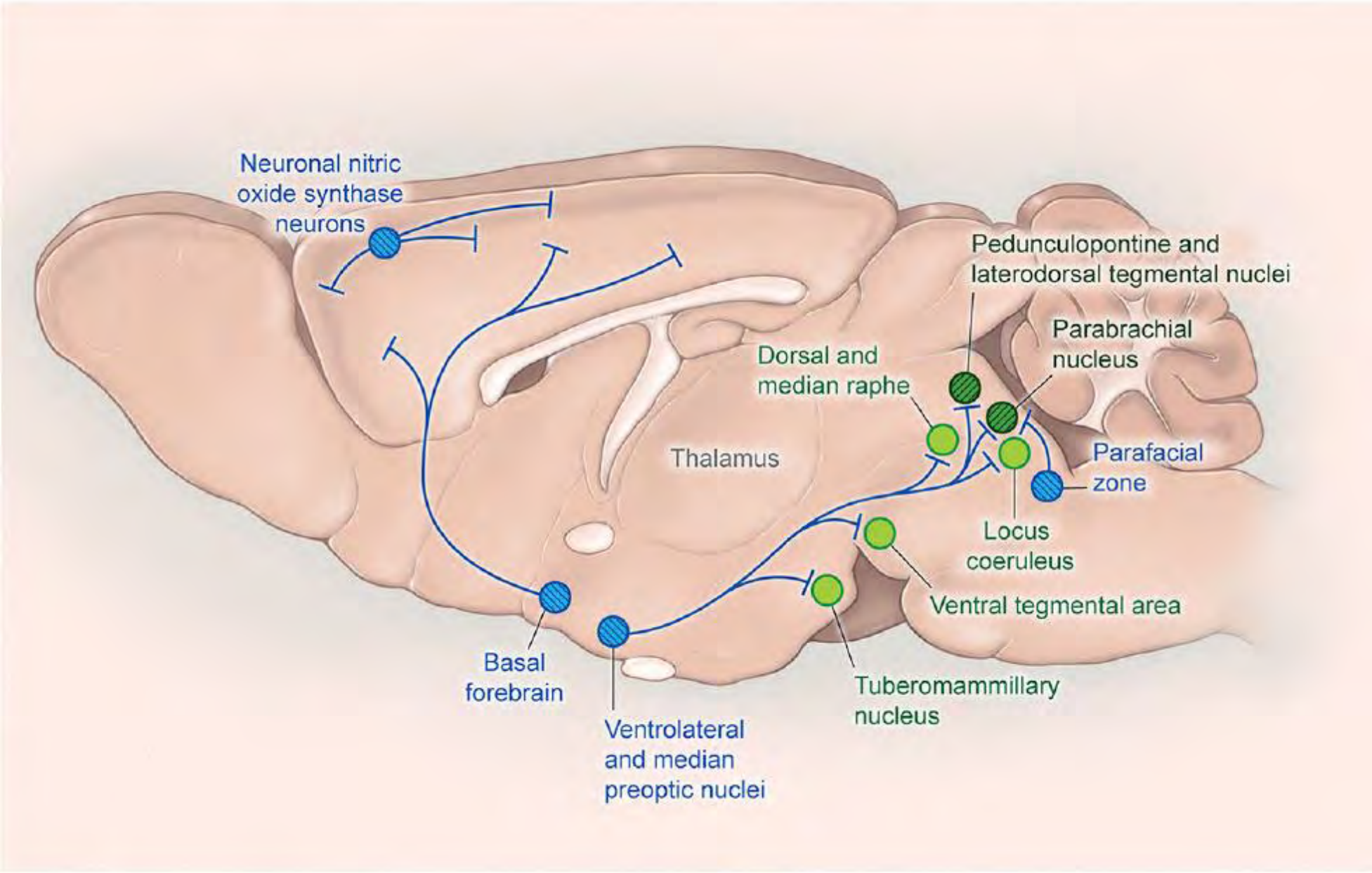
Neuron 201722;93: 747-765.



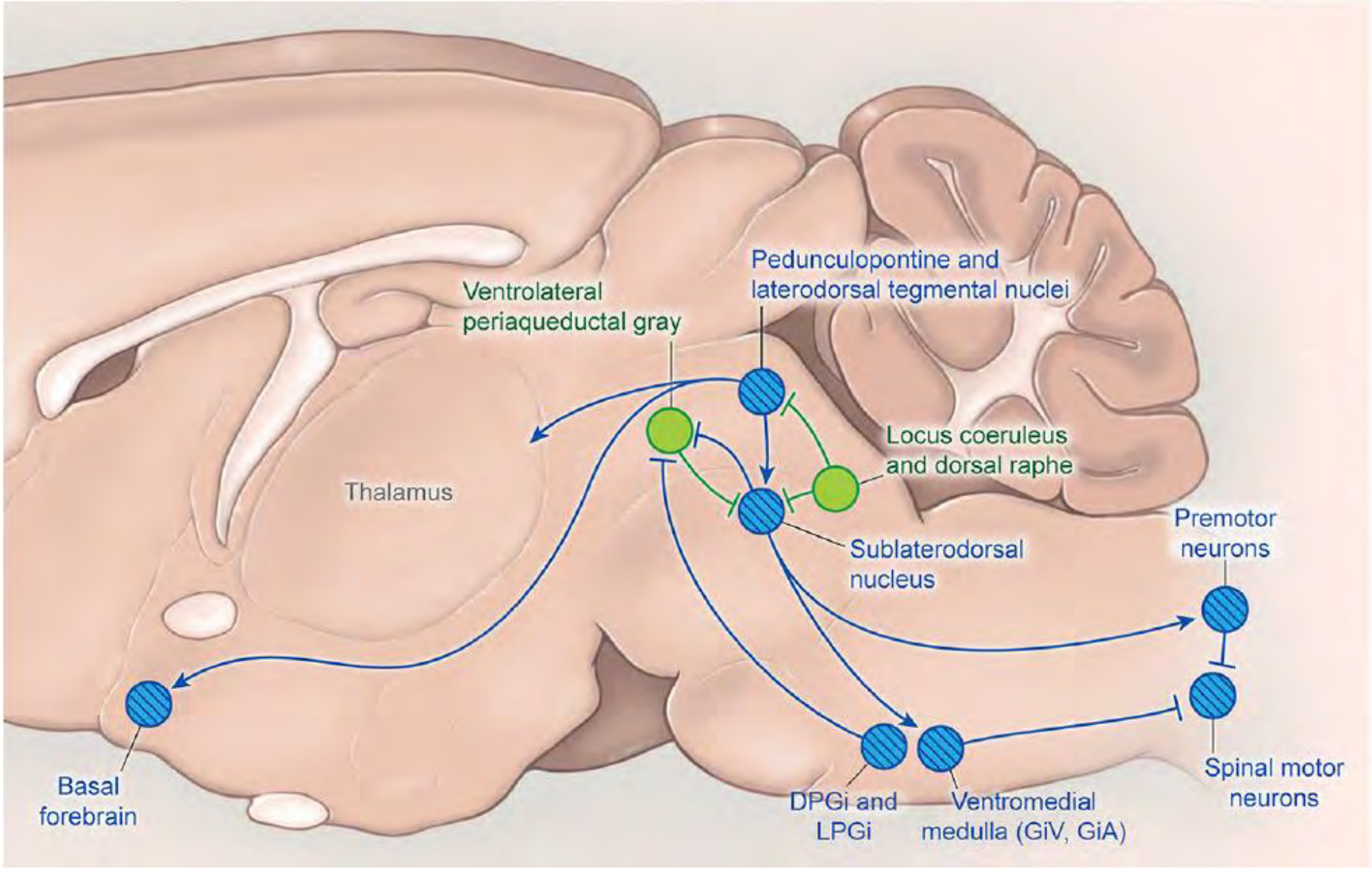
Orexin


Pedunculopontine and
laterodorsal tegmental nuclei
Parabrachial
nucleus
Dorsal and
median raphe
Thalamus
Locus coeruleus
Orexin
Ventral tegmental area
Basal
forebrain
Tuberomammillary
nucleus
Hypothalamus

NREM


Neuronal nitric oxide synthase neurons
Pedunculopontine and laterodorsal tegmental nuclei
Parabrachial nucleus
Dorsal and median raphe
Thalamus
Parafacial zone
Locus coeruleus
Ventral tegmental area
Basal forebrain
Ventrolateral and median preoptic nuclei
Tuberomammillary nucleus

REM

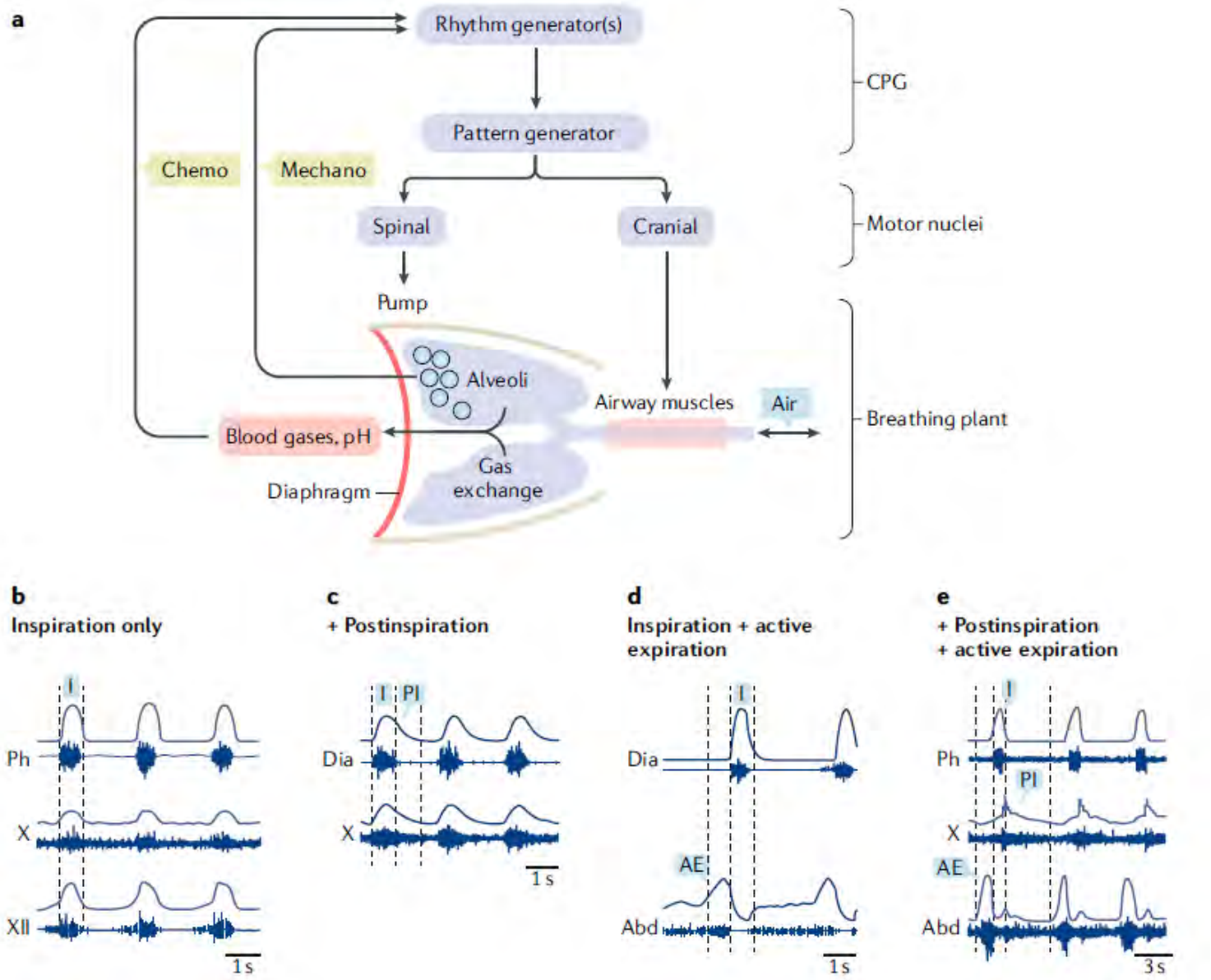

Ventrolateral
periaqueductal gray
Pedunculopontine and
laterodorsal tegmental nuclei
Locus coeruleus
and dorsal raphe
Thalamus
Sublaterodorsal
nucleus
Premotor
neurons
Basal
forebrain
DPGi and
LPGi
Ventromedial
medulla (GiV, GiA)
Spinal motor
neurons

The central autonomic network

- An integral component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, pain, and behavioral responses essential for survival
- Anterior cingulate, insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla
- Multiple inputs including nucleus of the tractus solitarius and humoral inputs relayed through the circumventricular organs
- Insular cortex and amygdala mediate high-order autonomic control
- The paraventricular nucleus control specific subsets of preganglionic sympathetic and parasympathetic neurons.

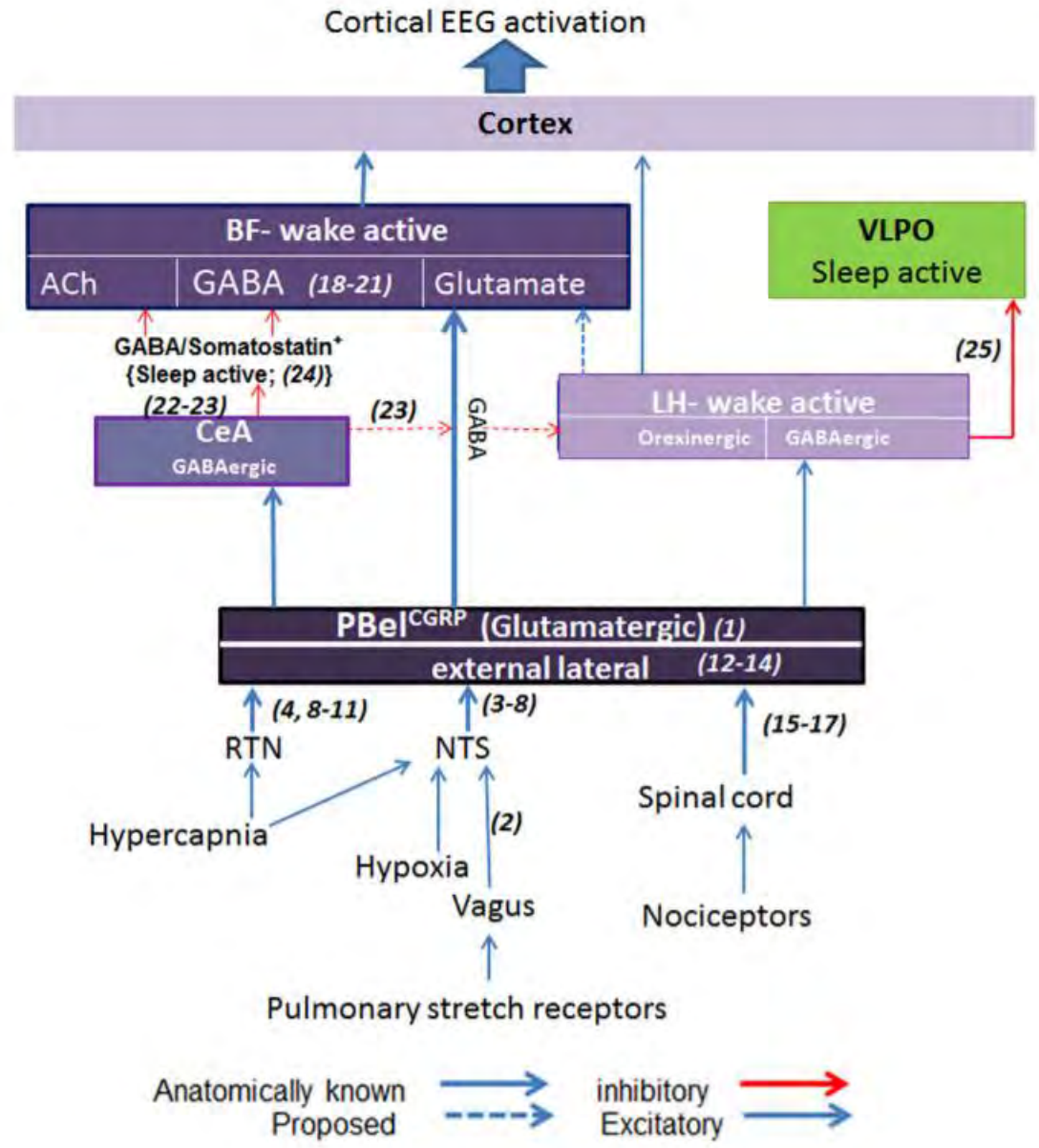
Respiratory Network

Nat Rev Neurosci 2018; 19:351-367



Hypercapnia

A Genetically Defined Circuit for Arousal from Sleep during Hypercapnia. Neuron 2017;96:1153-1167



Respiratory network dysfunction

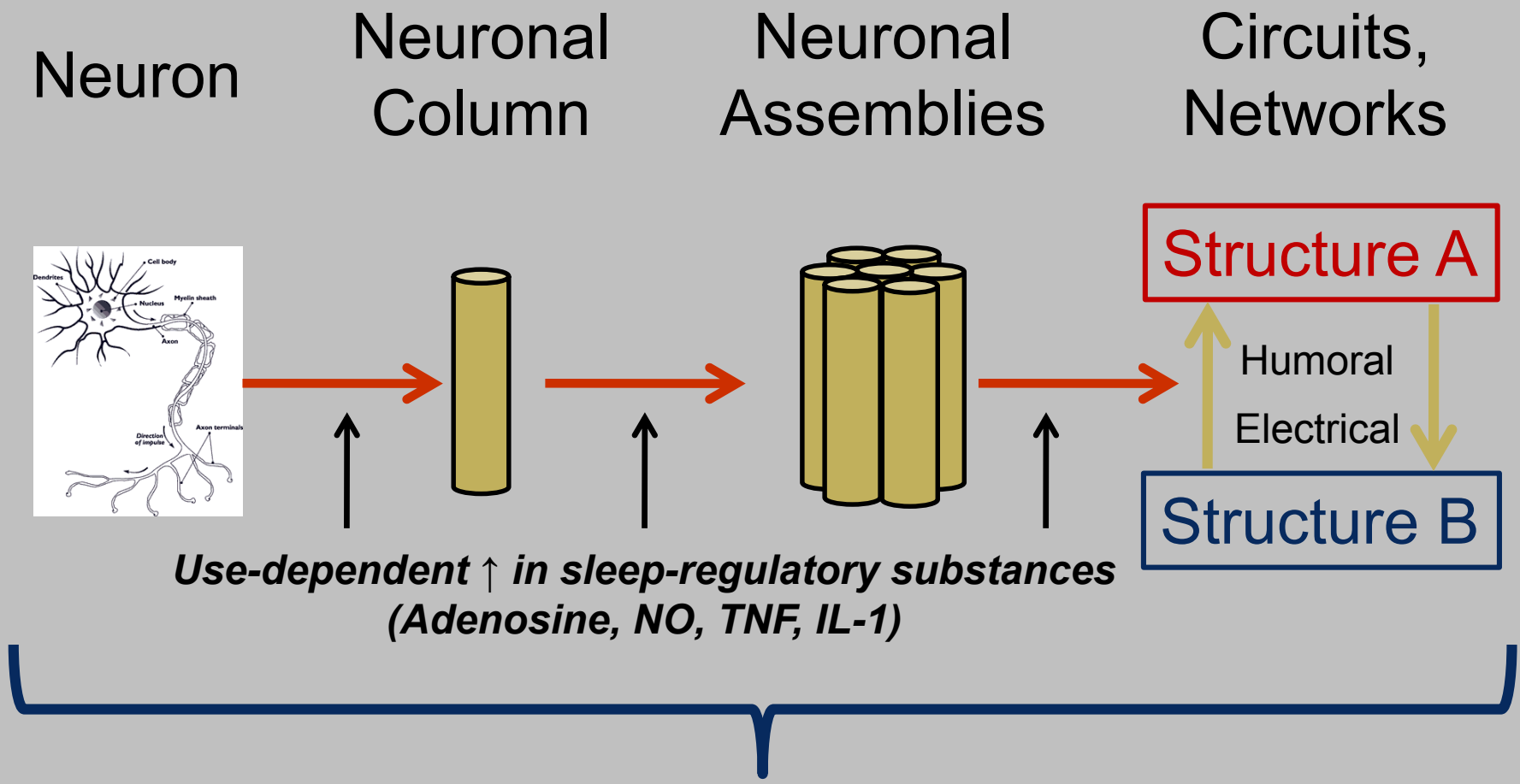
- Respiratory generative (examples)
  - Central congenital hypoventilation
  - Acquired hypoventilation
  - High spinal cord injury, syringomyelia
  - Motor neuron disease
- Respiratory control
  - Upper airway: negative pressure reflex (anesthesia)
  - High loop gain sleep apnea
- Cardiorespiratory interactions
  - Sinus arrhythmia
  - Cardiorespiratory synchronization
  - Respiratory-triggered arrhythmia

Thalamocortical network

- No need to spend much time on this for a sleep medicine audience
- Thalamocortical cell conductance (including hyperpolarization activated spike), reticular thalamic nucleus, spindles, 1-4Hz delta
- Spindles could be analogous to a 5G cell network
- The SO synchronizes and aggregates spindles, which are hyperlocal
- Spindles carry or enable information transfer but may also be a biological glue
- Certainly benzodiazepines increase spindling and increase network cohesion
- However, increased spindling is not necessary to increase cohesion

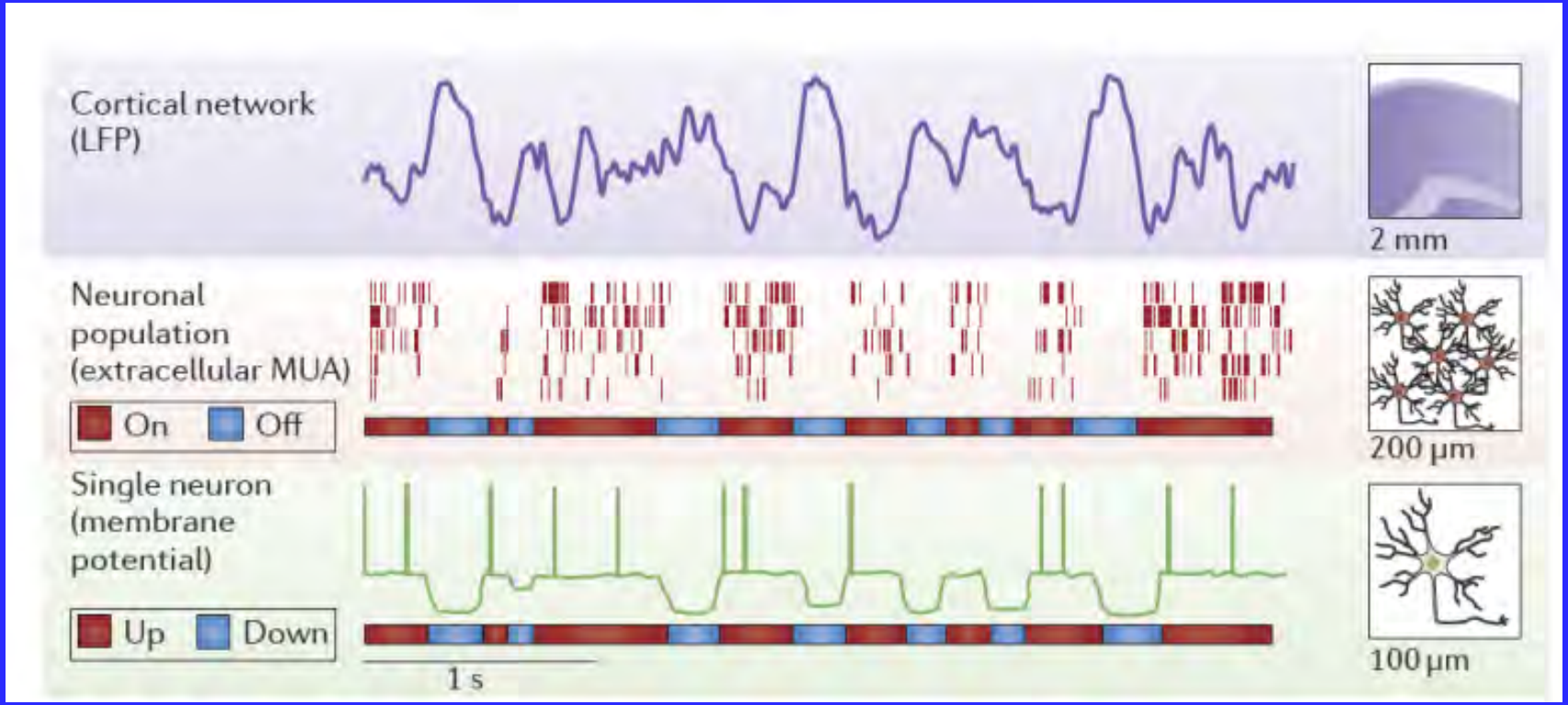
Lets talk about the cortical network

“Local sleep” and systemic sleep

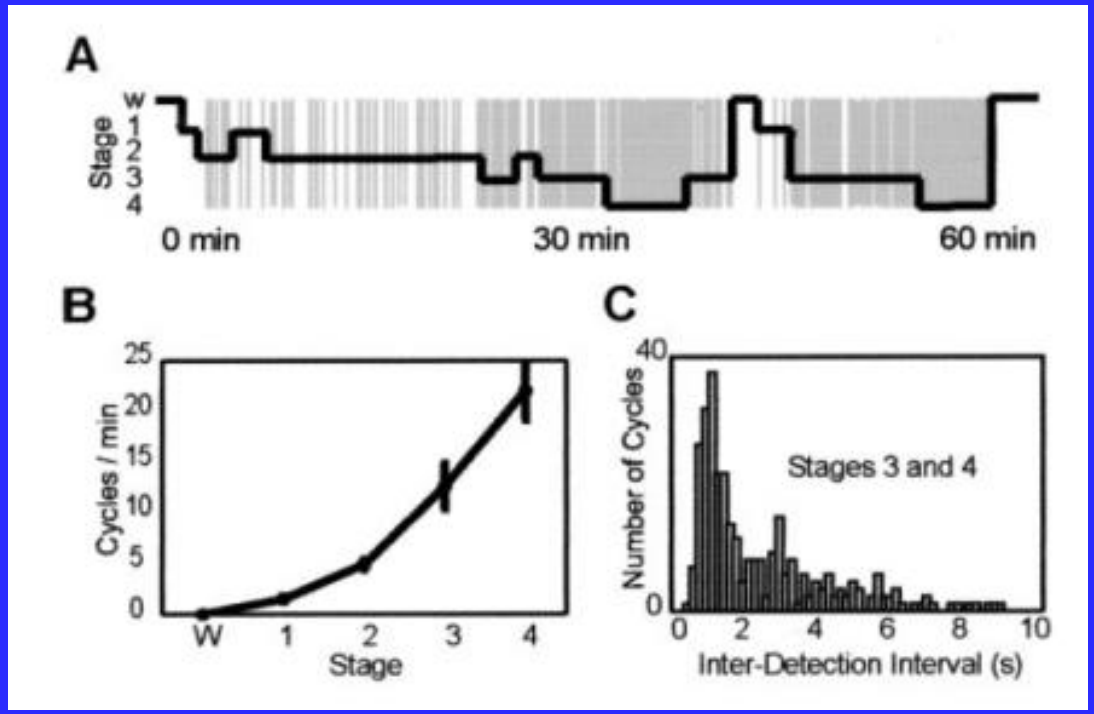


Krueger et al., *Nature Reviews Neuroscience* 2008; 9:910-919

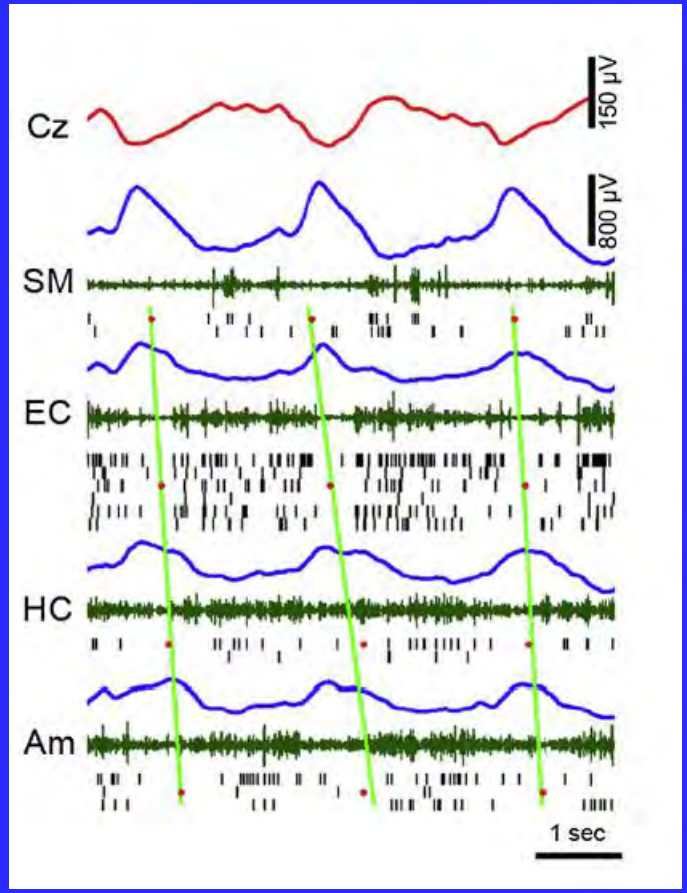
The “up” and “down” (on/off) states of the cerebral cortex. It permeates the whole brain.



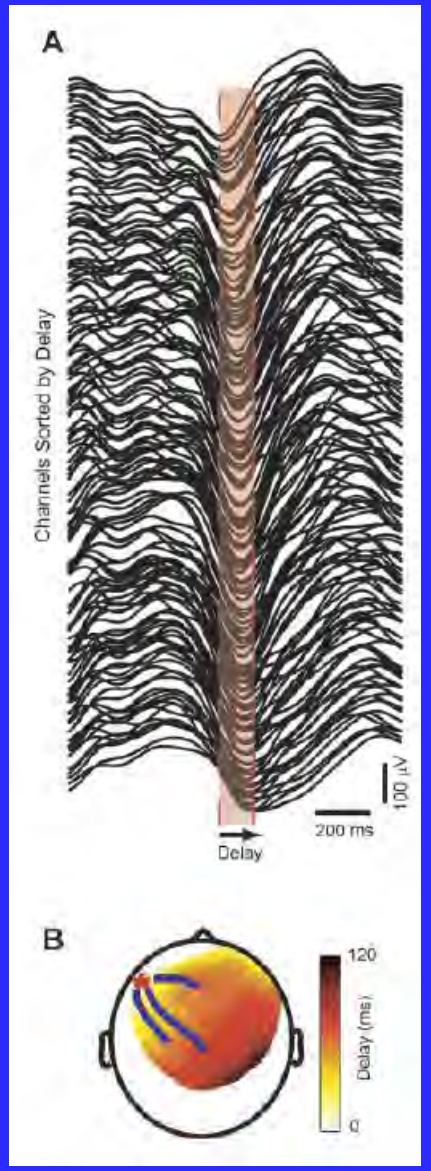
The Slow Oscillation (SO) builds in frequency and spatial extent as sleep starts and deepens. Below-high within individual stability.

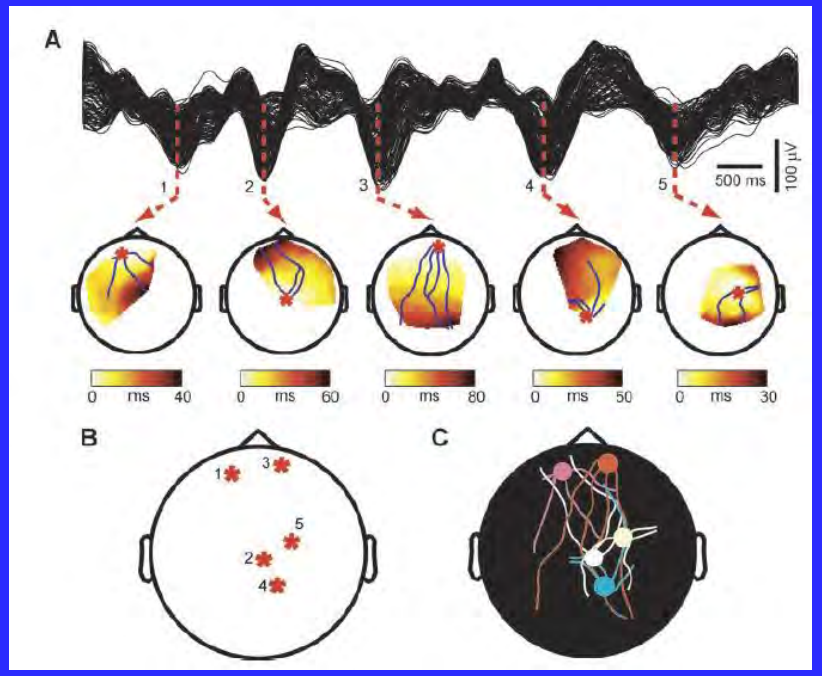


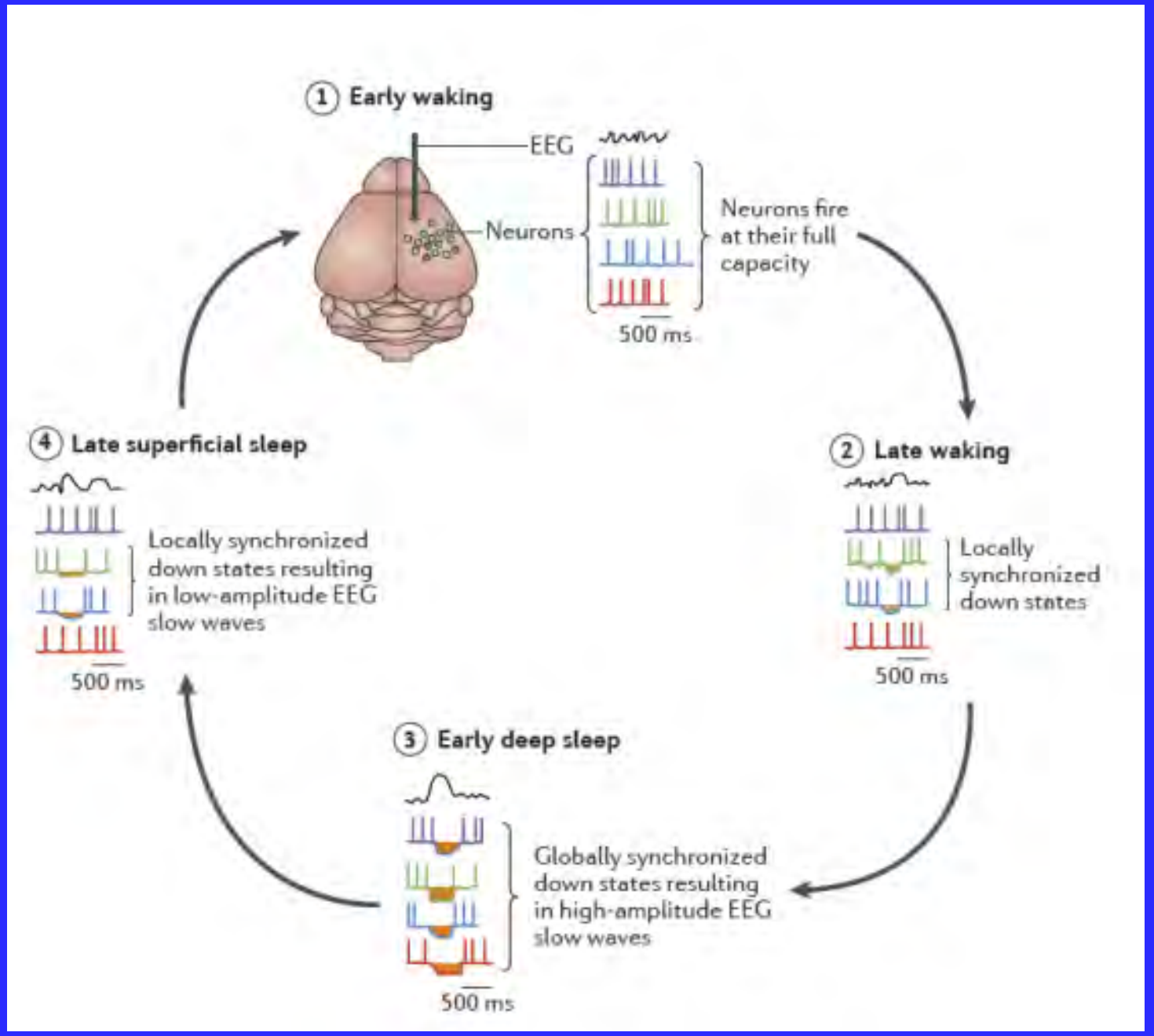
SO travels



More SO traveling wave characteristic






1 Early waking
EEG
Neurons
Neurons fire at their full capacity
500 ms
2 Late waking
Locally synchronized down states
500 ms
3 Early deep sleep
Globally synchronized down states resulting in high-amplitude EEG slow waves
500 ms
4 Late superficial sleep
Locally synchronized down states resulting in low-amplitude EEG slow waves
500 ms

RLS/PLMS network

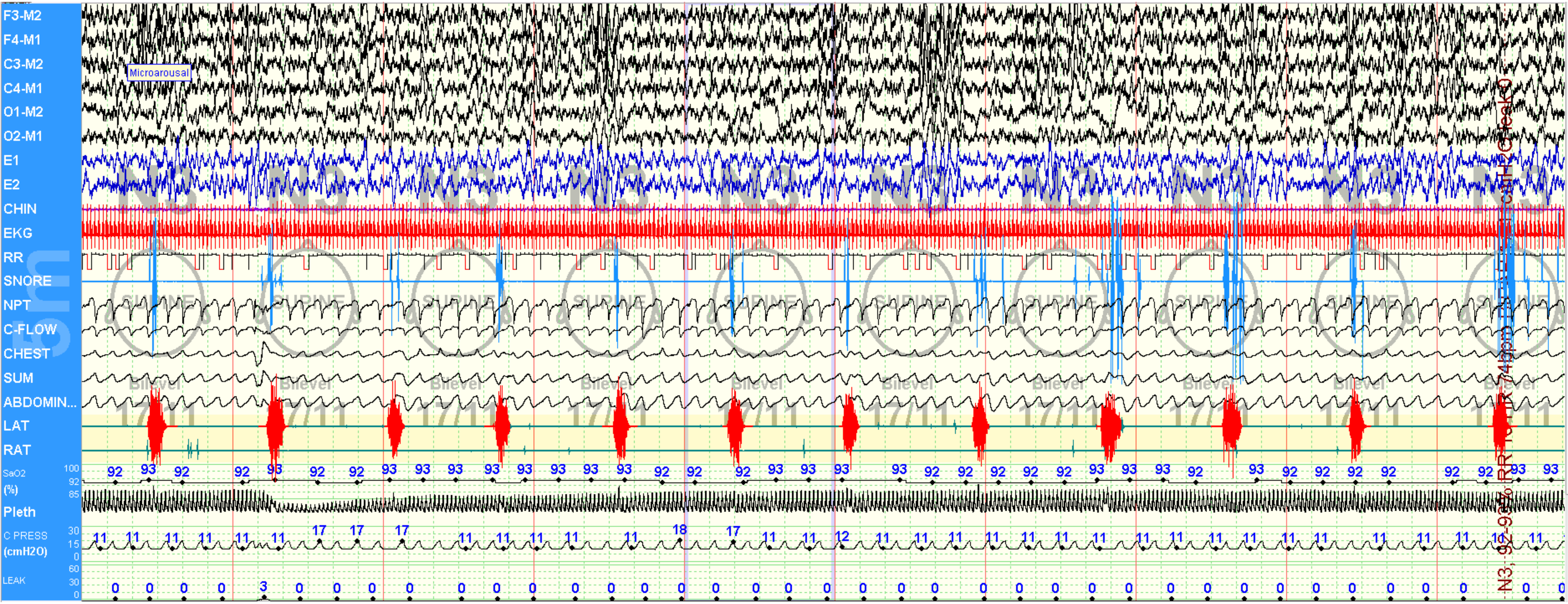
- Through targeted ablation in rats, a potential role for corticospinal, cerebellorubro-spinal, and hypothalamic A11 dopaminergic systems in the development of RLS-like movements during sleep. Targeted lesions in select basal ganglia structures revealed a major role for nigrostriatal dopamine, the striatum, and the external globus pallidus (GPe) in regulating RLS-like movements, in particular pallidocortical projections from the GPe to the motor cortex. Lesions of the corticospinal tract at the C1 level, the motor cortex and somatosensory cortex all induced excessive periodic motor activation in NREM sleep.

Guo CN, Yang WJ, Zhan SQ, Yang XF, Chen MC, Fuller PM, Lu J. Targeted disruption of supraspinal motor circuitry reveals a distributed network underlying Restless Legs Syndrome (RLS)-like movements in the rat. Sci Rep 2017;7:9905.

RLS/PLMS network

- Tightly linked to autonomic activation
- Can occur with or without cortical arousal, but degree of arousal correlates with degree of blood pressure surge
- Increasing evidence of adverse cardiovascular outcomes in RLS
- PLMS is often severe in heart failure and renal failure patients - likely contributes to pathological nocturnal hemodynamics

PLMS


F3-M2
F4-M1
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
EKG
RR
SNORE
NPT
C-FLOW
CHEST
SUM
ABDOMIN...
LAT
RAT
SaO2 (%)
Pleth
C PRESS (cmH2O)
LEAK
Microarousal

Consequences of the time of night distribution of the SO glue

- First half of the night is less vulnerable to sleep disruption
- Arousability of sleep increases as the night progresses
- Successful insomnia treatment likely improves effective SO glue
- Critical points of weakness occur regularly across the night
- SO breaks down with poor cortical health, or excessive subcortical drivers, or perhaps inadequate subcortical NREM driving
- Genetic factors associated with sleep resilience likely impact SO
- Insomnia pharmacotherapy is from one view illogical
  - Greatest help needed when SO is weakest (second half of night)

Central autonomic network

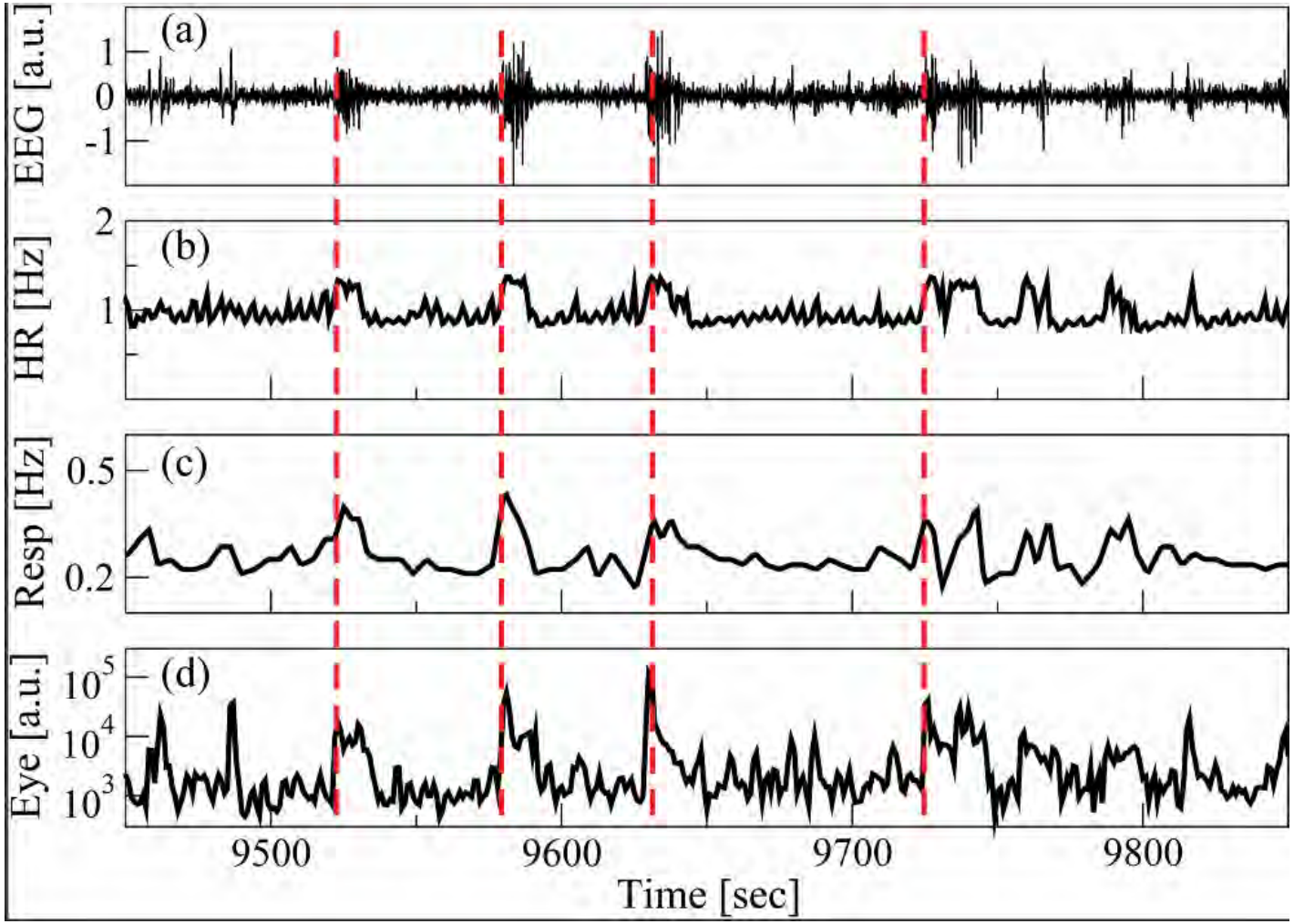
- Components include insular cortex, ventromedial prefrontal cortex and anterior cingulate (Cortical control of the autonomic nervous system. Exp Physiol 2014;99:326-331)
- Tight functional links to amygdala, hypothalamic paraventricular nucleus, parabrachial nucleus
- Reliably activated by pain, visceral input
- Activation associated with muscle sympathetic nerve activity

How can we measure the network health of sleep?

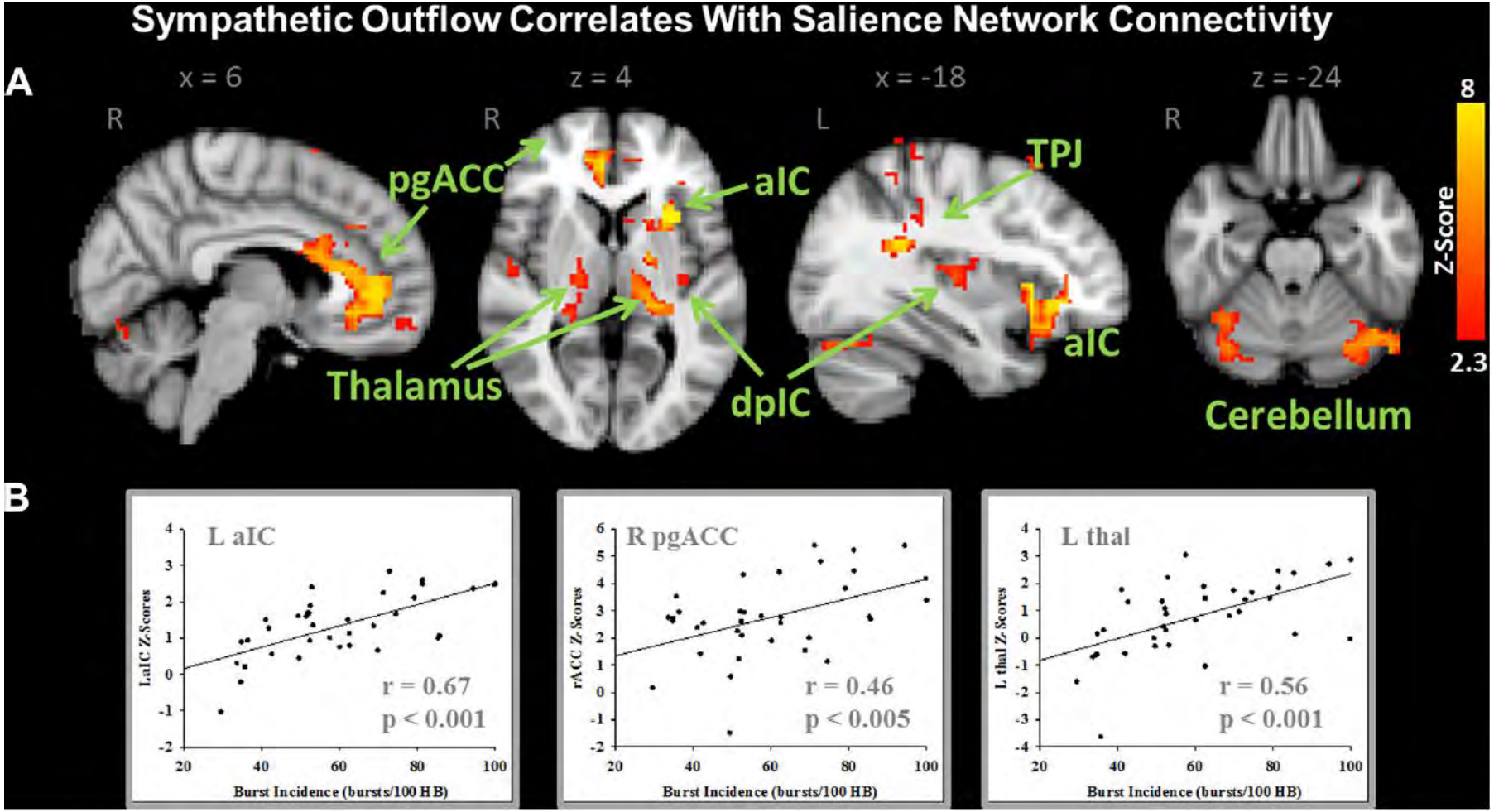
Technologies and approaches to measure sleep networks

- Classic polysomnography scoring does not directly estimate integrated network health though signals can be analyzed
- Functional MRI
- High density EEG polysomnography
- Depth recordings + ECG, hemodynamics, respiration
- Analysis of coupled oscillations
- Time delay stability

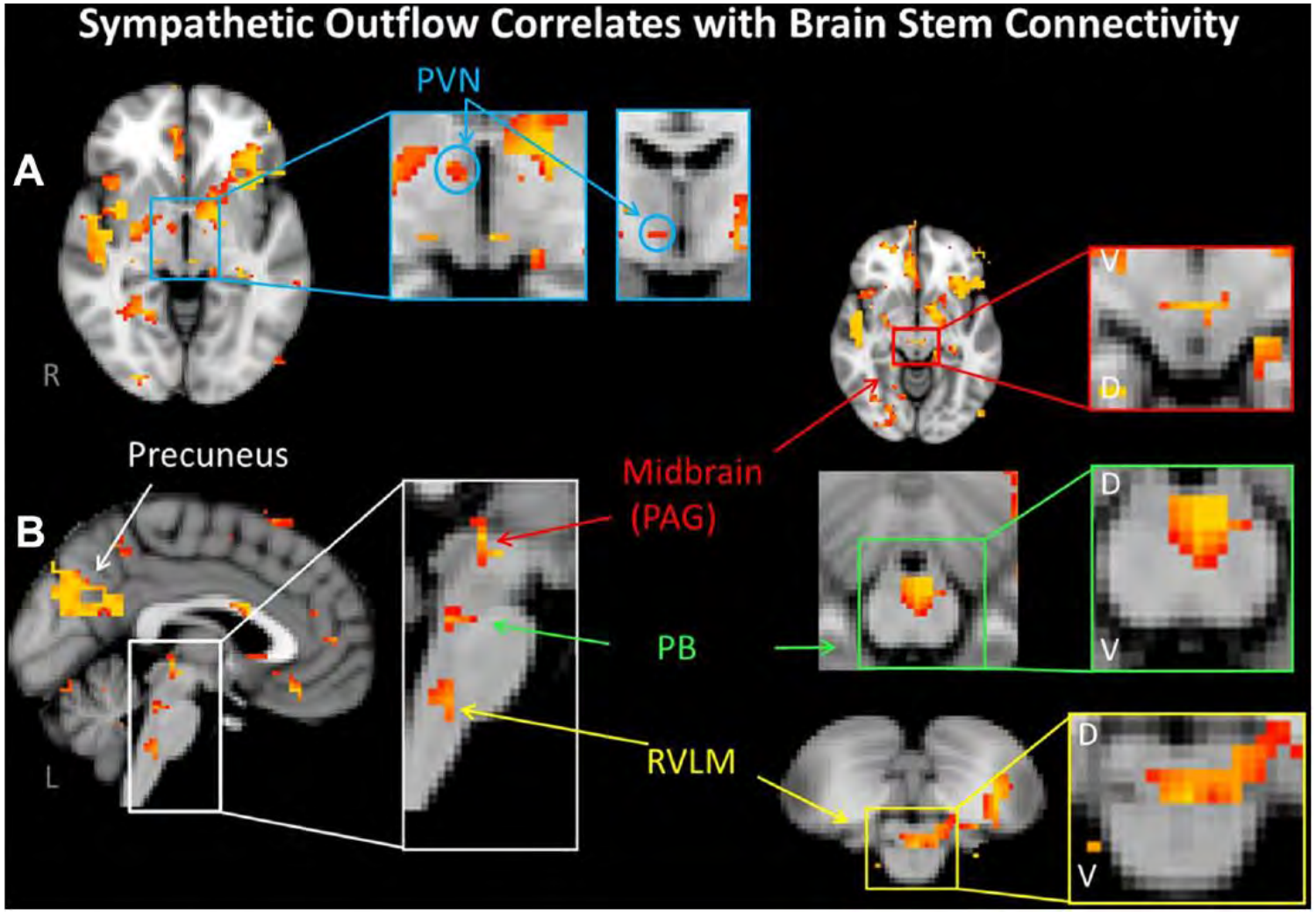
Time delay stability



Functional MRI estimation of brain networks



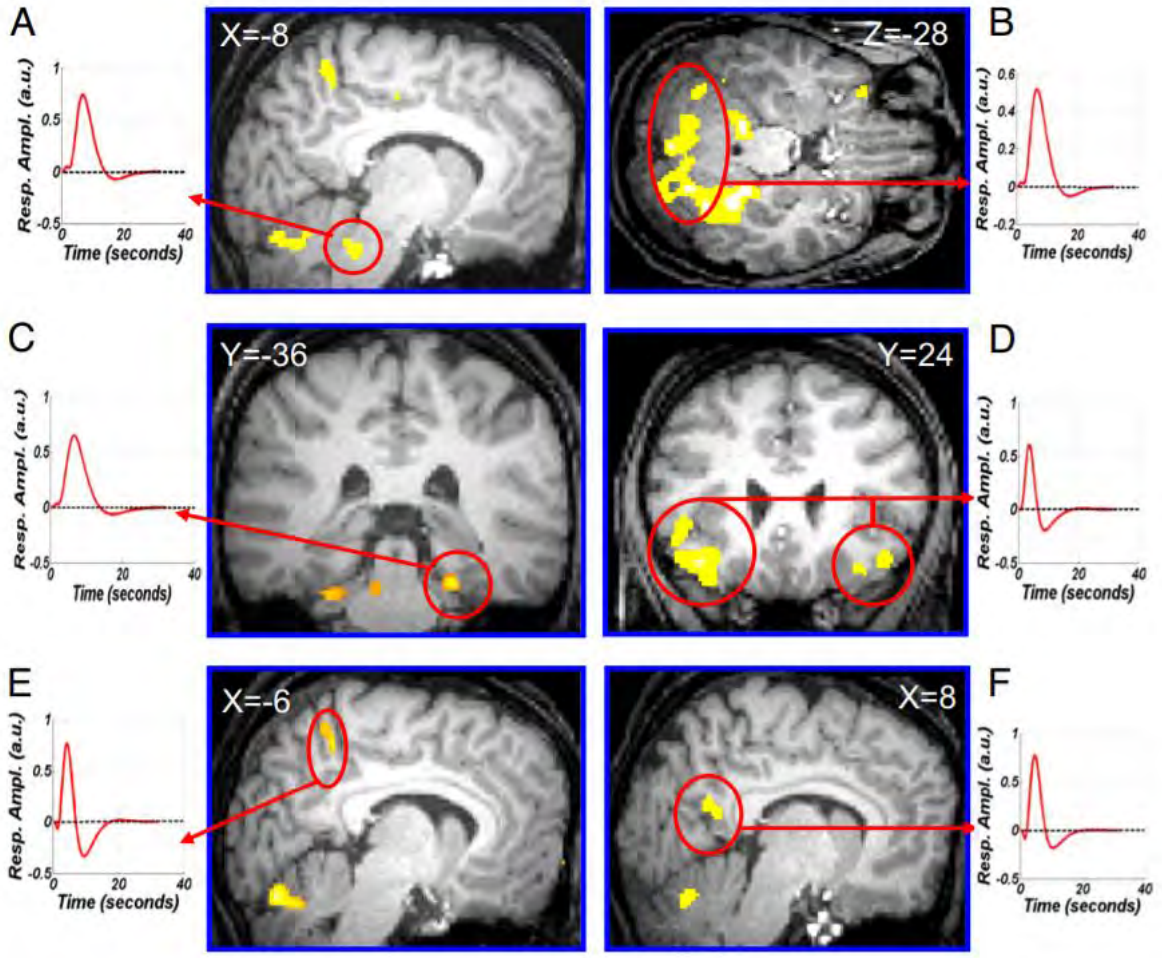
Functional MRI estimation of brain networks



fMRI of SO and delta waves (PNAS 15160–15165, September 30, 2008, vol. 105)

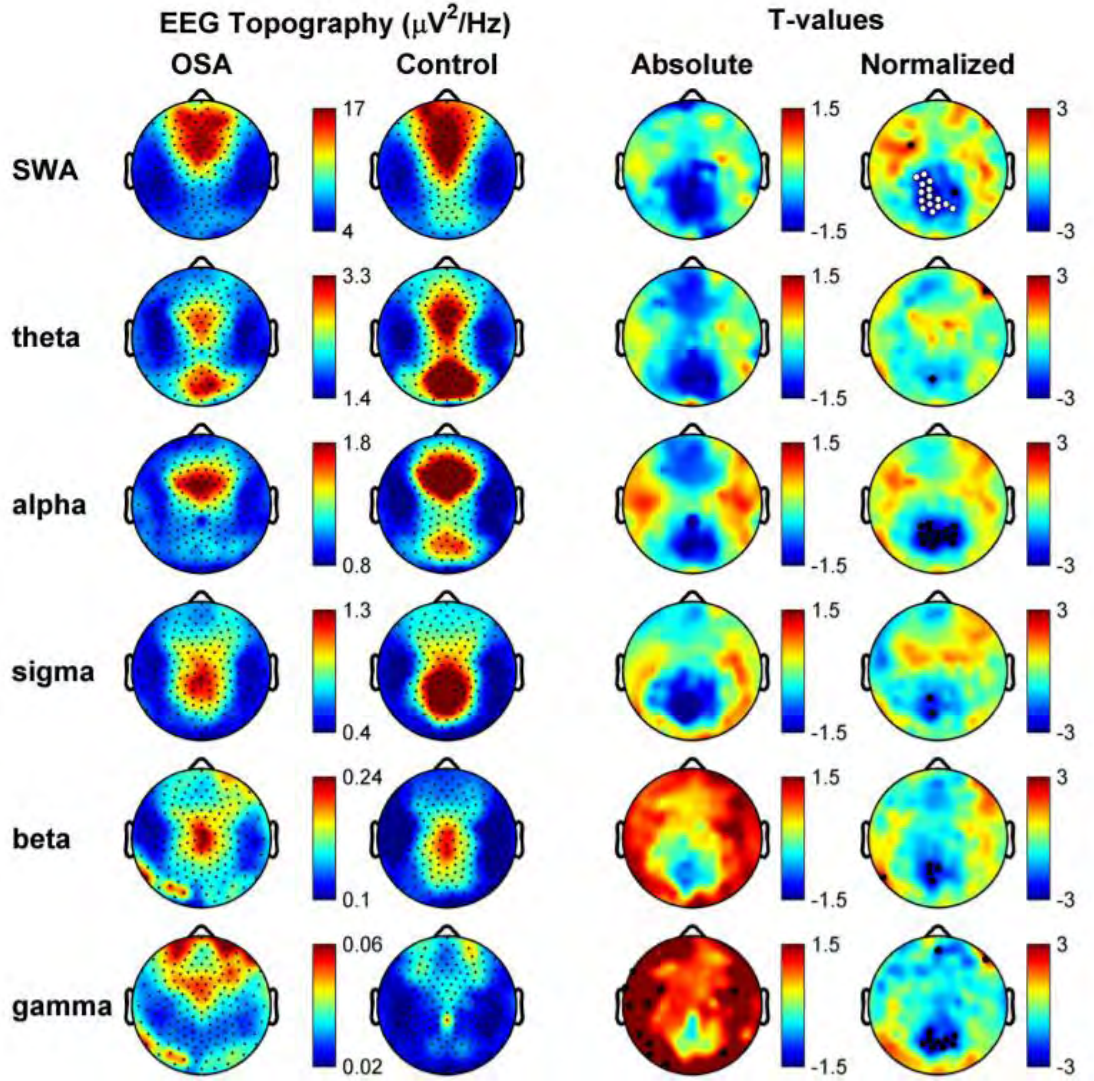
- Using simultaneous EEG and event-related functional magnetic resonance imaging (fMRI), the transient changes in brain activity consistently associated with slow waves (>140 μV) and delta waves (75–140 μV) during SWS in 14 non-sleep-deprived normal human volunteers
- Significant increases in activity were associated with these waves in several cortical areas, including the inferior frontal, medial prefrontal, precuneus, and posterior cingulate areas. Compared with baseline activity, slow waves are associated with significant activity in the parahippocampal gyrus, cerebellum, and brainstem, whereas delta waves are related to frontal responses

fMRI of SO and delta waves (PNAS 15160–15165, September 30, 2008, vol. 105)



High density EEG polysomnography

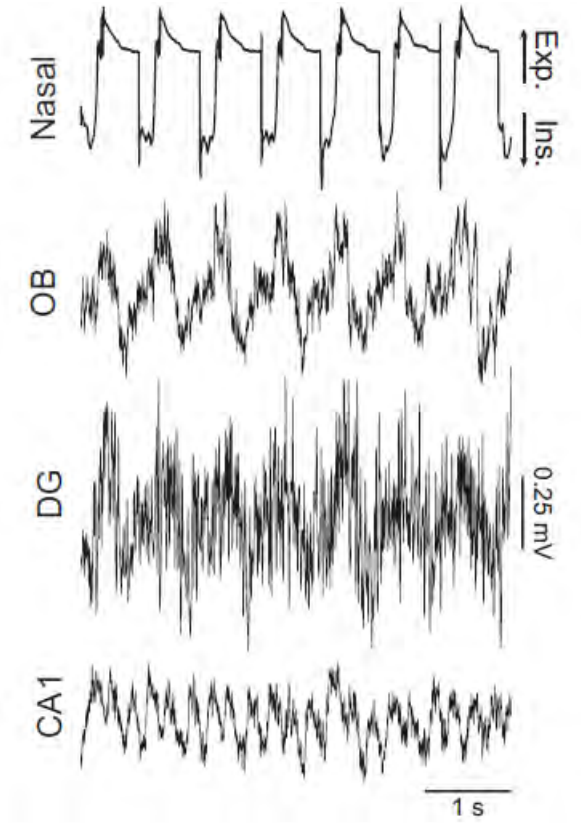
Regional Reductions in Sleep Electroencephalography Power in Obstructive Sleep Apnea: A High-Density EEG Study. SLEEP 2014; 37: 399–407.



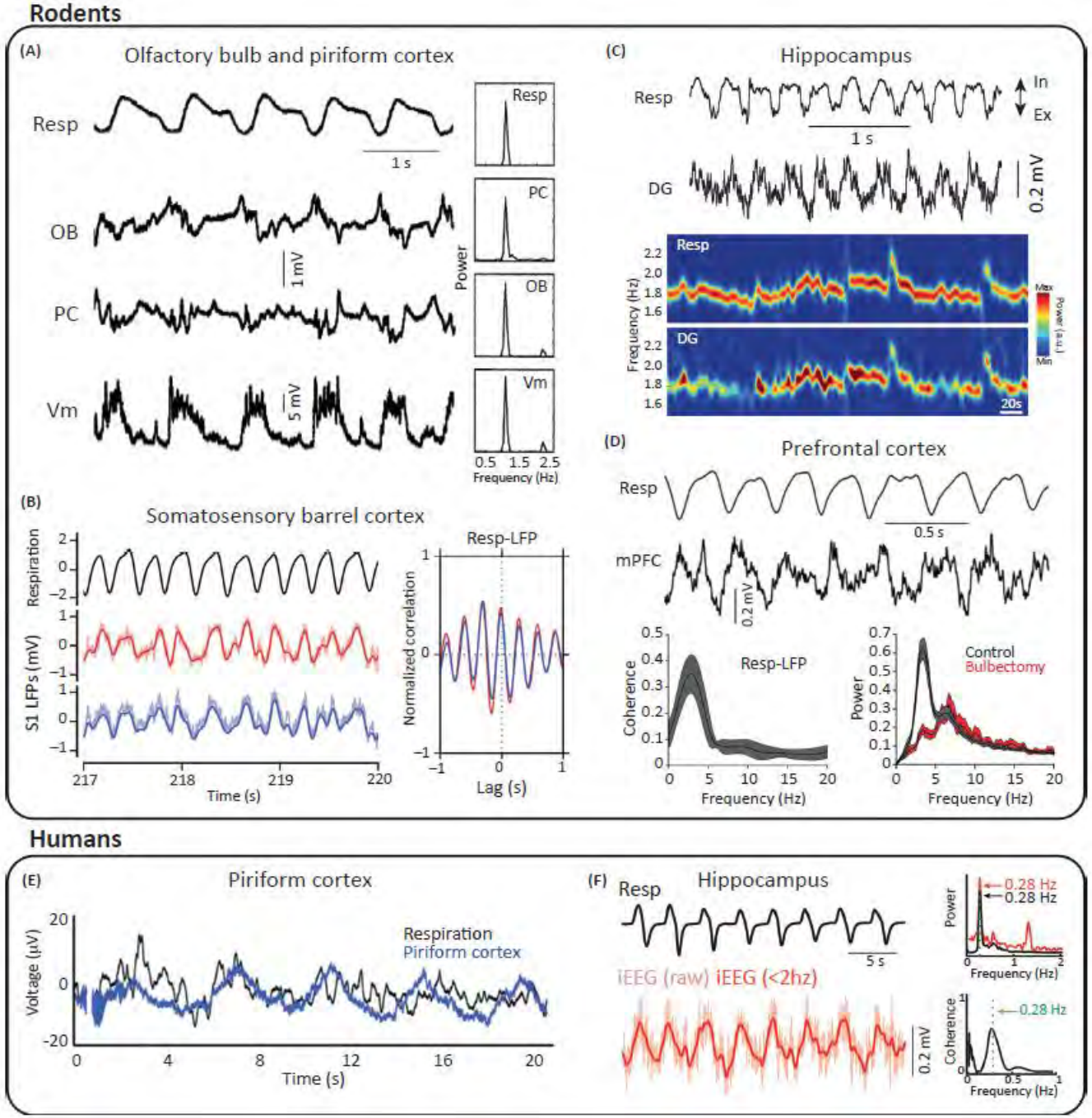
End of Part I, Part II starts

Respiration is deeply encoded in the brain network

- **A Respiration-Coupled Rhythm in the Rat Hippocampus Independent of Theta and Slow Oscillations. Lockmann ALV, et al. J Neurosci 2016;36:5338 –5352.**



Respiration-Entrained Brain Rhythms Are Global but Often Overlooked.
Trend Neurosci 2018;41:186-197.



What can Network Physiology do for sleep science and sleep medicine

- What is this sleep glue that hold disparate oscillators in synchrony? We have a “binding problem” in sleep. How does this inform consciousness?
- What is the minimum unit of sleep to perform function? That is, is there a universal law of tolerance to sleep fragmentation/arousals?
- Why are certain individuals with incredibly fragmented sleep asymptomatic, and vice versa?
- Can the “disruption grade” of pathology be quantified?
- Is a “network map” of sleep useful in clinical practice?

Syndromes of sleep pathology

- Insomnia
- Hypersomnia
- Excessive daytime sleepiness
- Parasomnia
- Restless legs/movements
- Circadian rhythm disorders

Large scale network influences and breakdowns

- Binding mechanisms
  - Slow oscillation
  - Cyclic alternating pattern
  - PGO waves
- Breakdown etiologies
  - Congestive heart failure
  - Atrial fibrillation
  - Severe traumatic brain injury
  - Treatment-resistant depression
  - Mania
  - Neurodegeneration

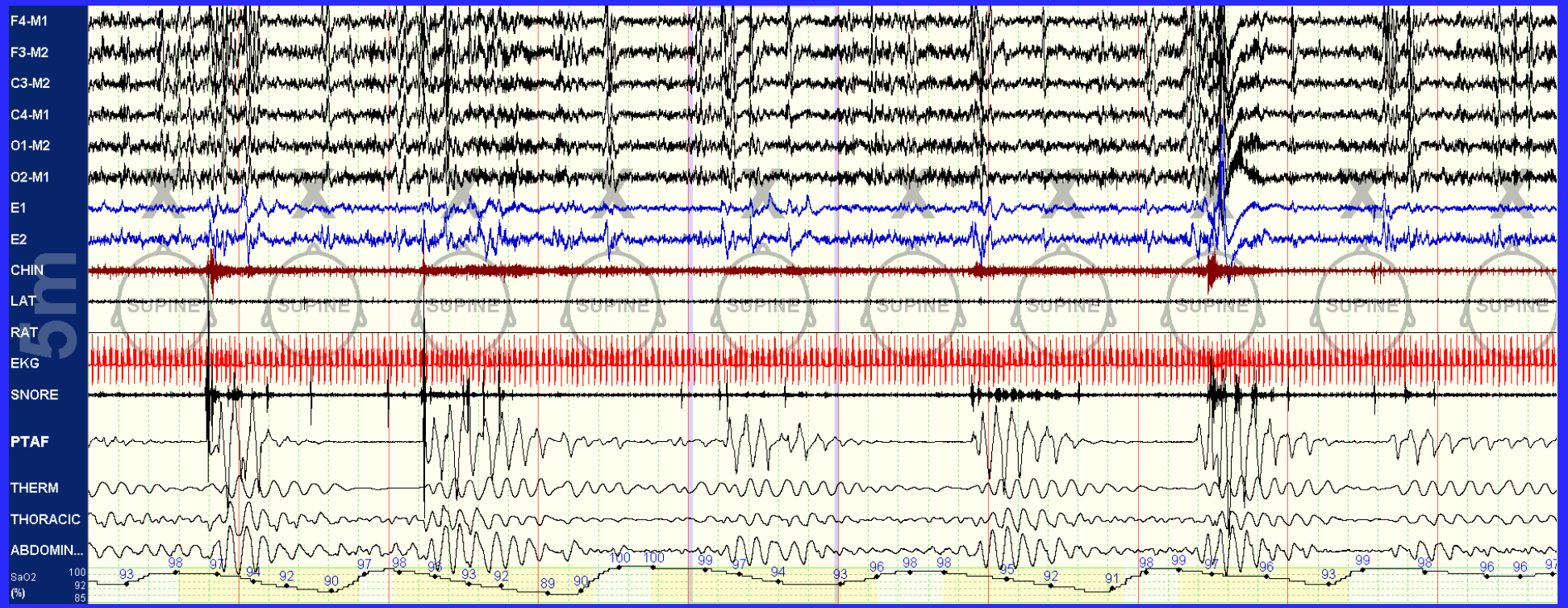
Network breakdown

- Cortical
  - Normally highly resilient and redundant (e.g. stroke)
  - Traumatic brain injury
  - Alzheimer’s disease, Parkinson’s disease
  - Epilepsy
- Thalamocortical network
  - Prion disease
  - Tumor
  - Stroke (including paramedian)
- Sleep-wake transition network
  - Insomnia (various driver mechanisms, including circadian)
  - Amygdala-based syndromes: anxiety, fear, PTSD
  - Pain, stress

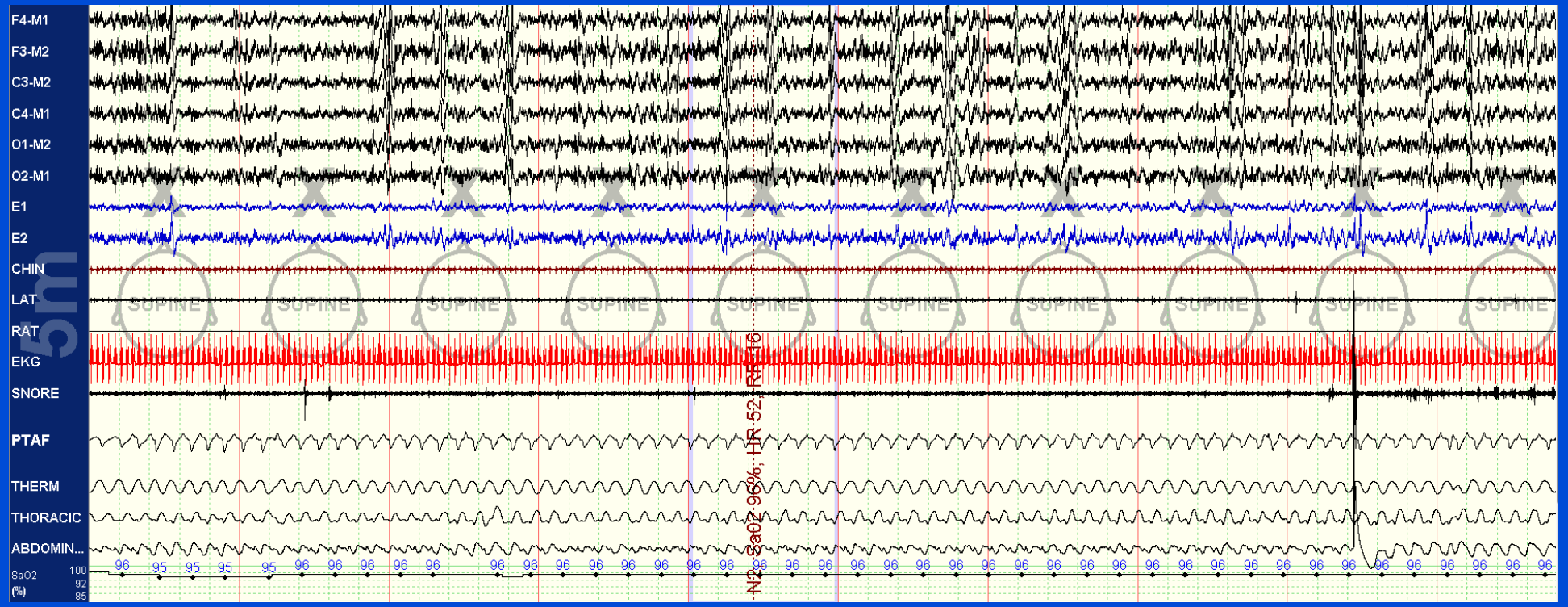
Network breakdown

- REM sleep network
  - RBD, PTSD, nightmares
- NREM sleep network
  - Sleepwalking, insomnia, depression
- Arousal network
  - Unstable
    - Bipolar, Kleine-Levin syndrome
  - Hypoactive
    - Coma, Persistent vegetative state, minimally conscious state
    - Anesthesia (all anesthetic agents are not equal, e.g., ketamine-xylazine results in greater glymphatic flow than isoflurane
  - Hyperactive
    - Extrinsic: pain, abnormal respiration
    - Intrinsic: PTSD, stress

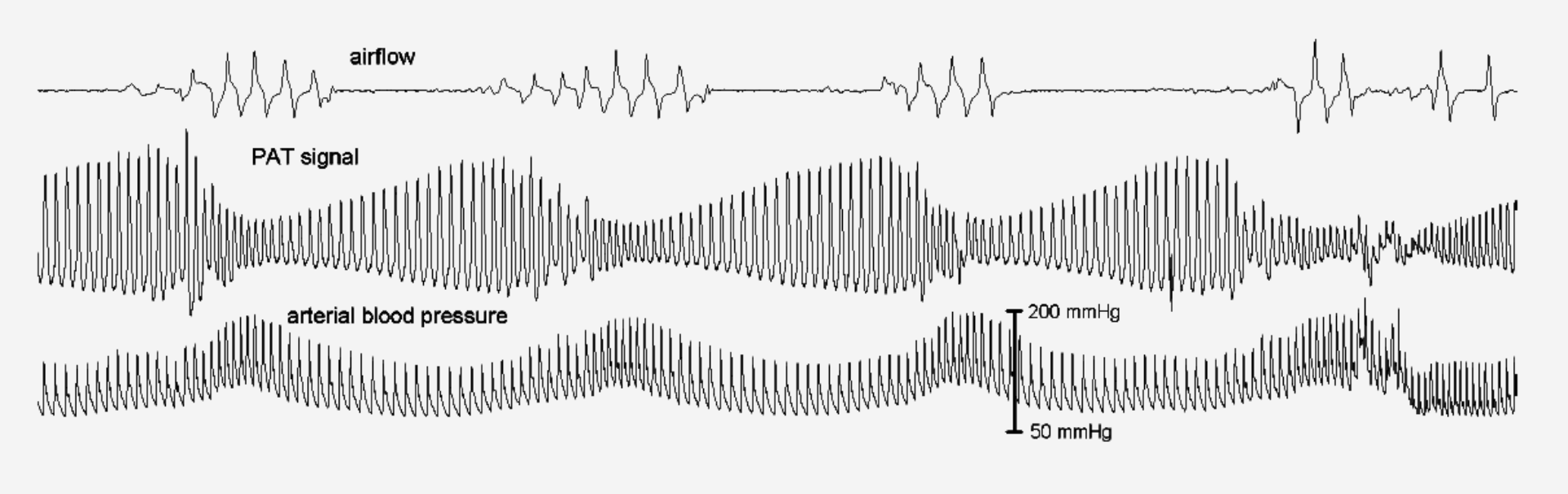
Coupled network oscillations



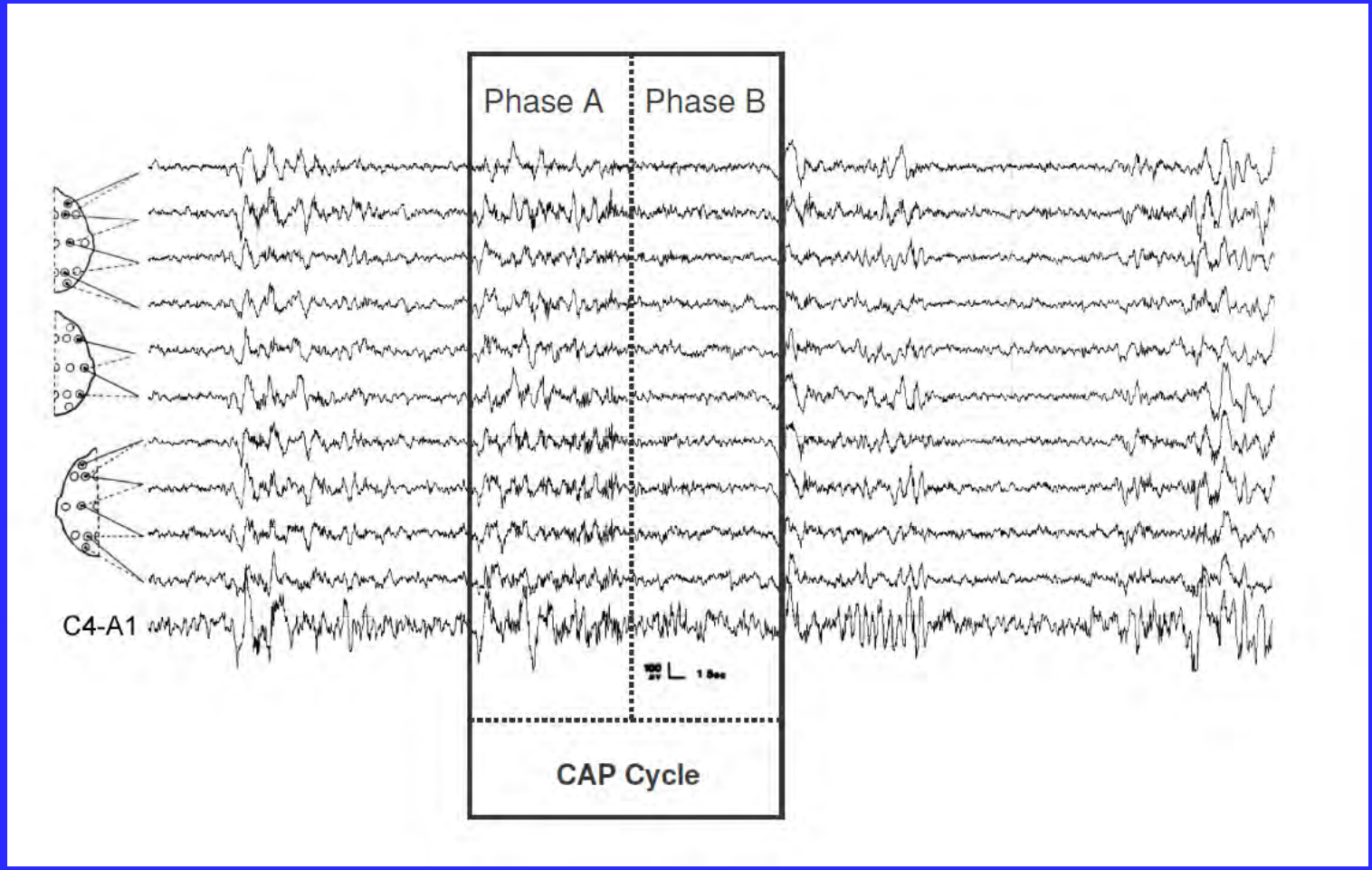
Stable NREM


F4-M1
F3-M2
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
LAT
RAT
EKG
SNORE
PTAF
THERM
THORACIC
ABDOMIN...
SaO2 (%)
100
92
85
SUPINE
N2 SaO2 96%, HR 52, RR 16

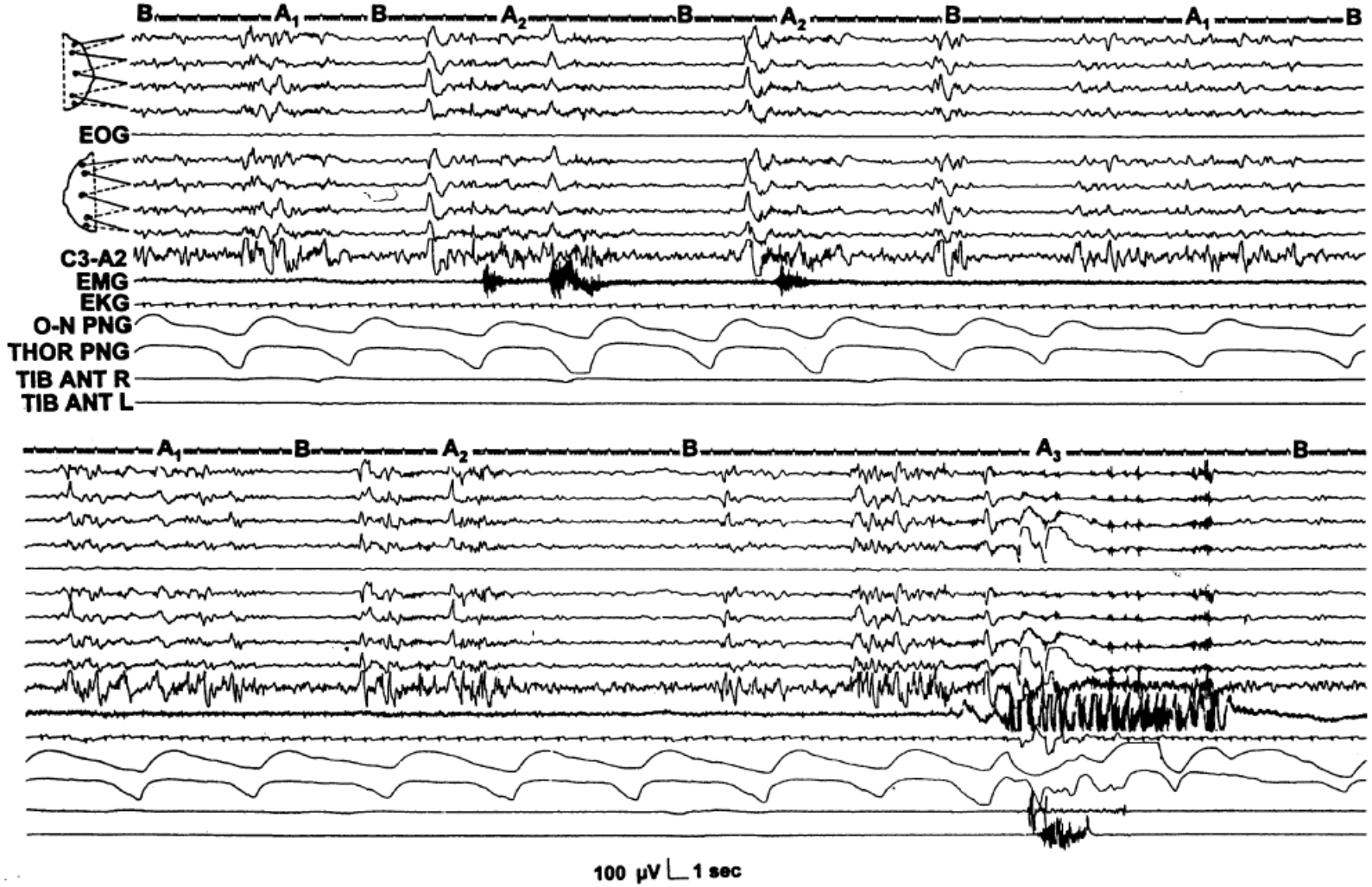
Multiple coupled sleep subsystems – respiration, autonomic drive, blood pressure



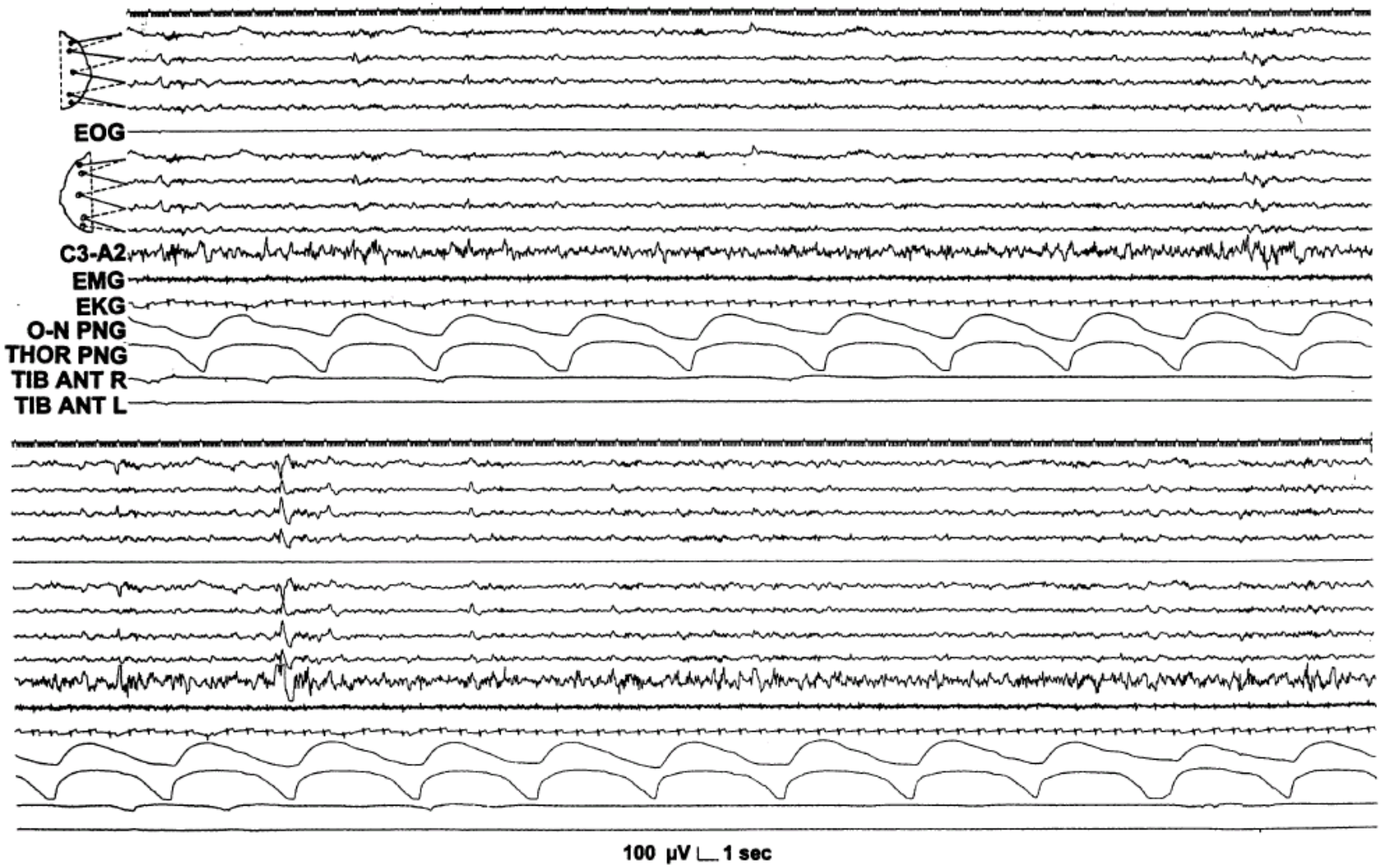
Cyclic Alternating Pattern (CAP)



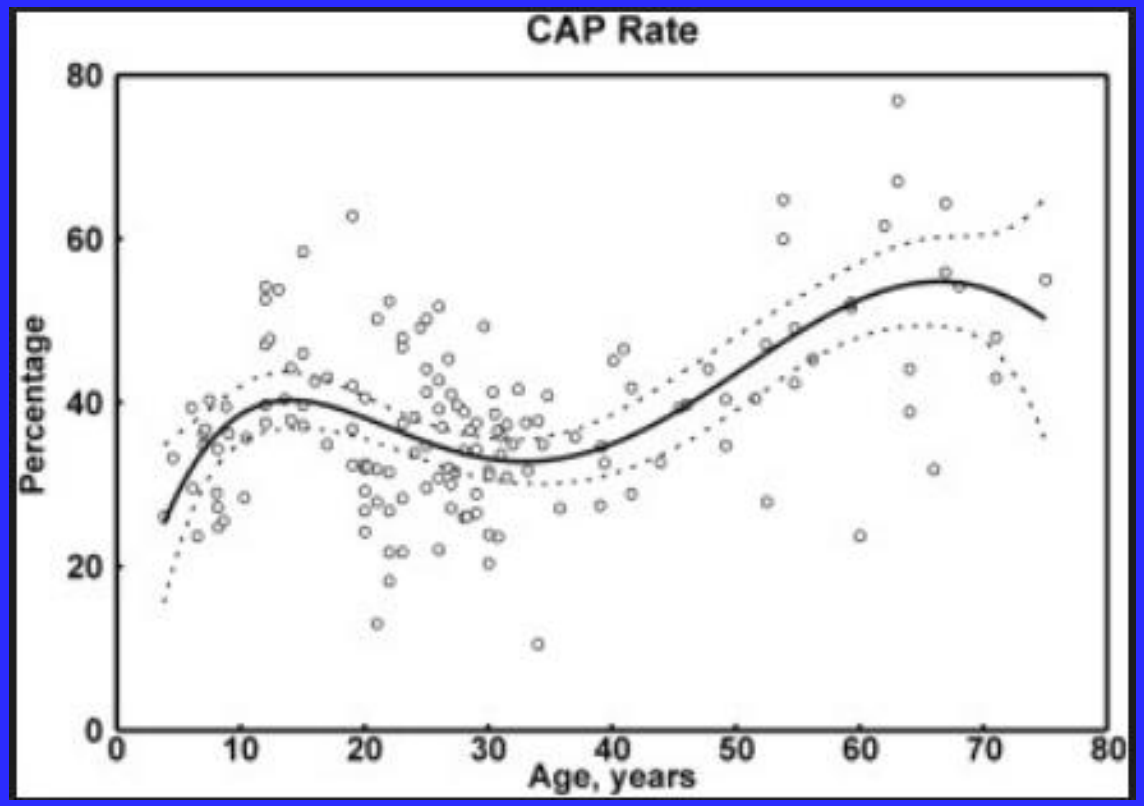
A period of CAP which can go on for tens of minutes, markedly amplified in disease



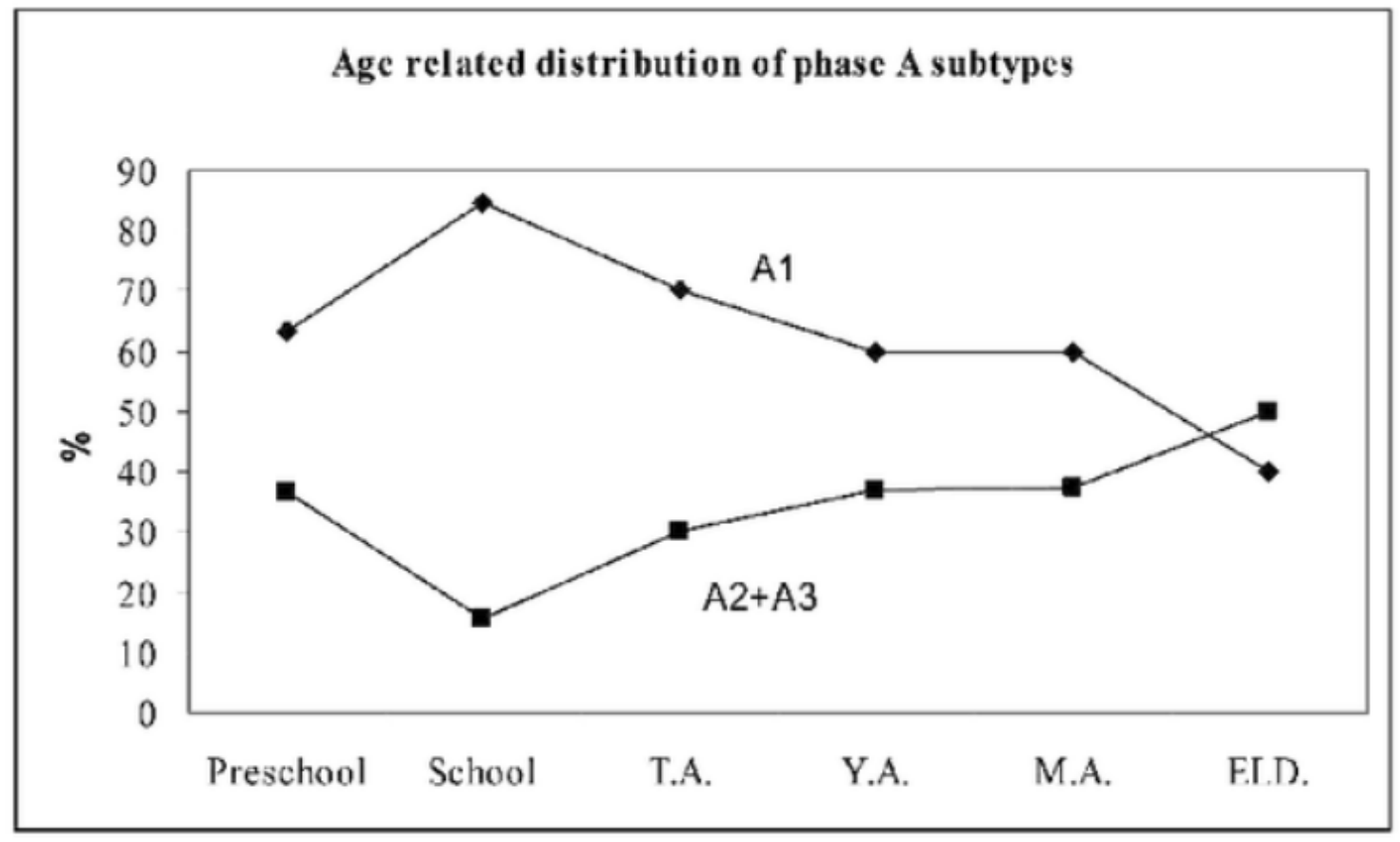
A period of EEG quiescence, which can go on for tens of minutes



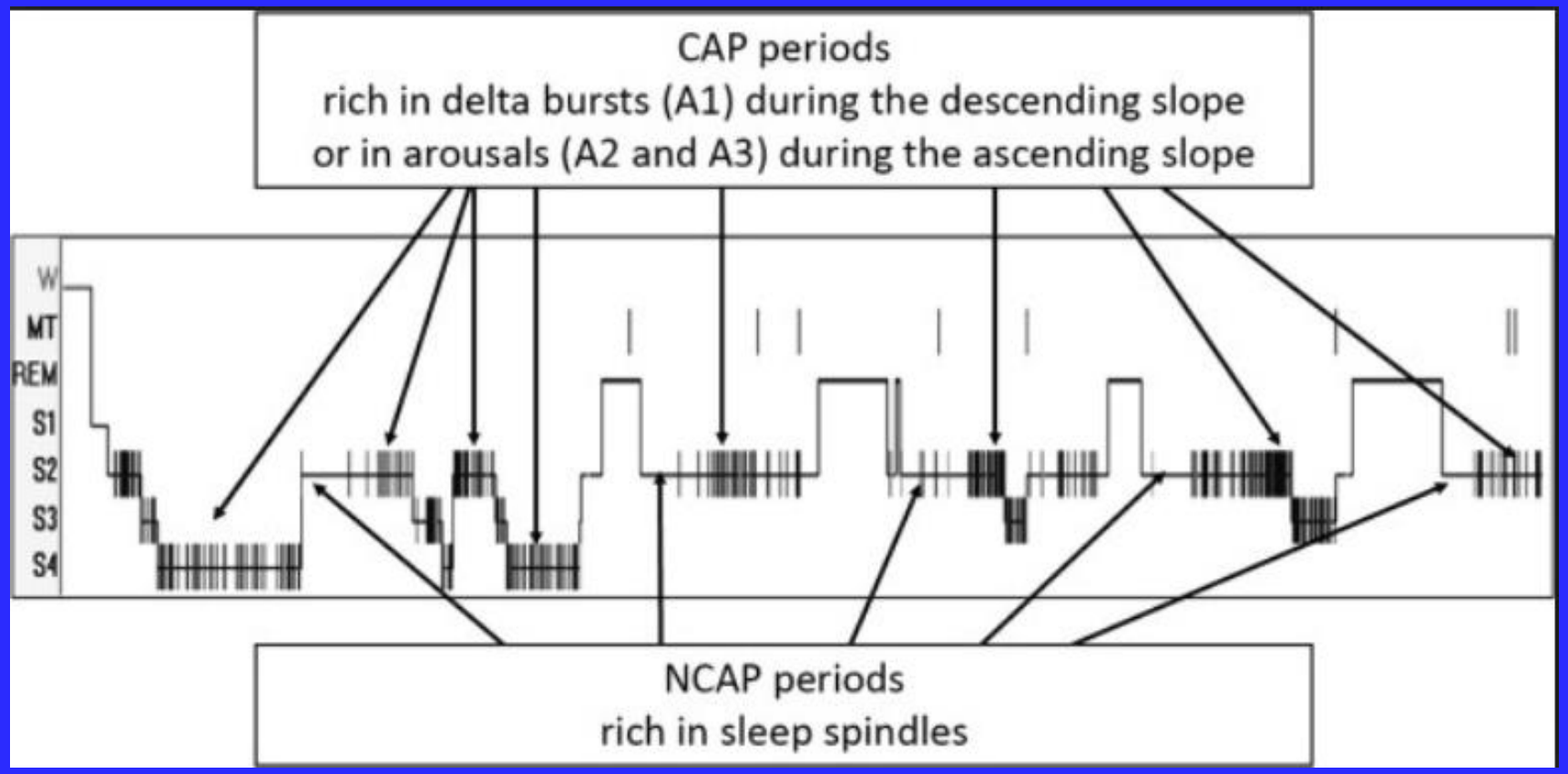
CAP and age


CAP Rate
Percentage
80
60
40
20
0
0
10
20
30
40
50
60
70
80
Age, years

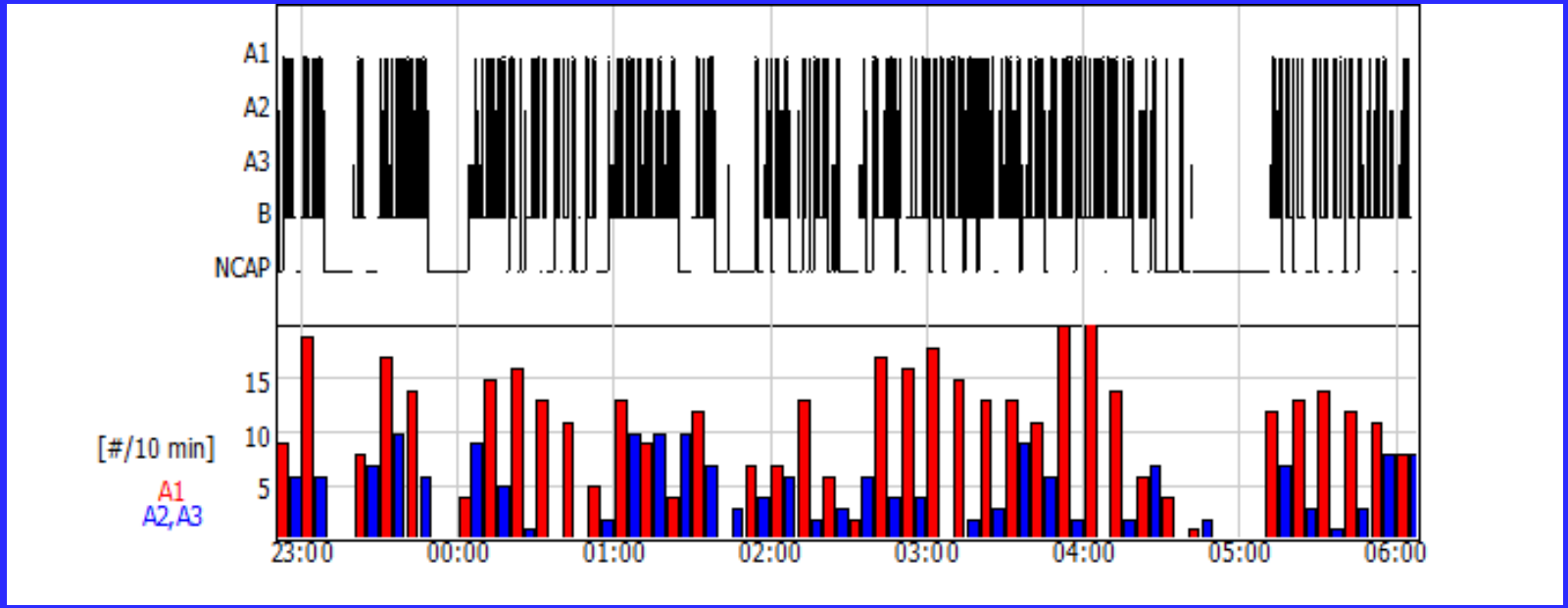
CAP subtypes and age



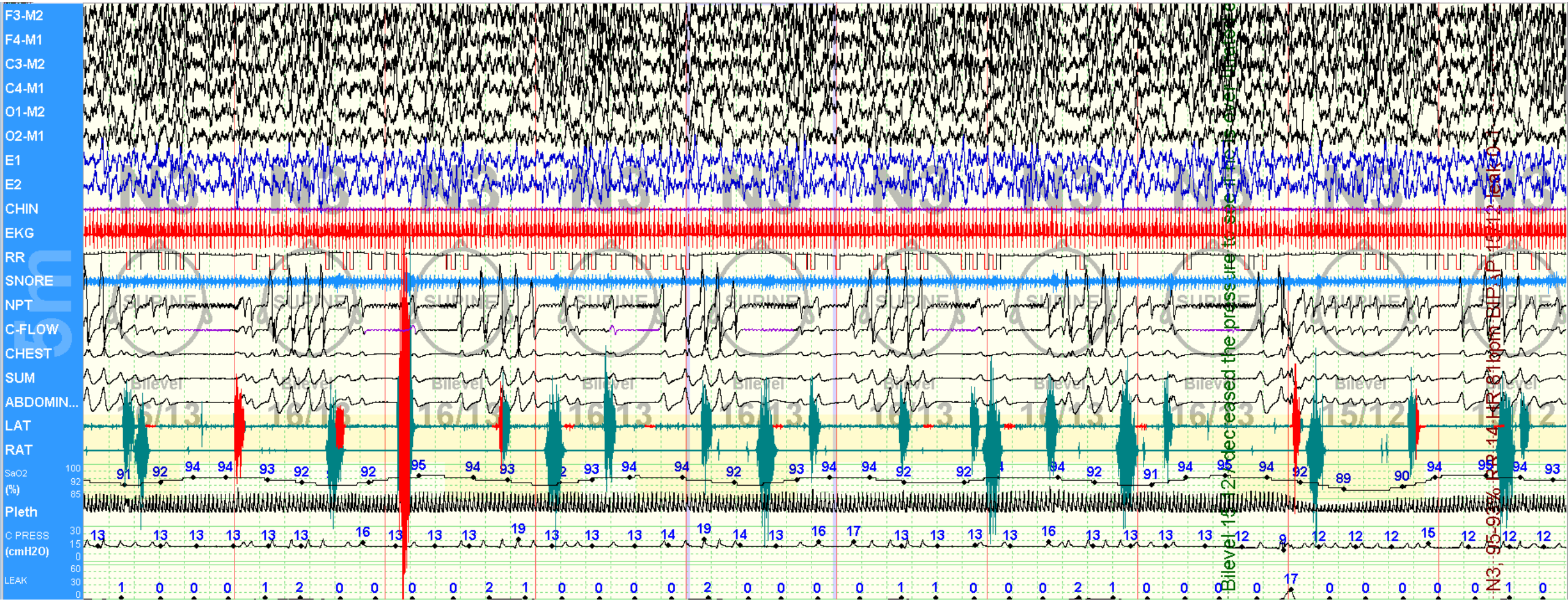
Capnogram

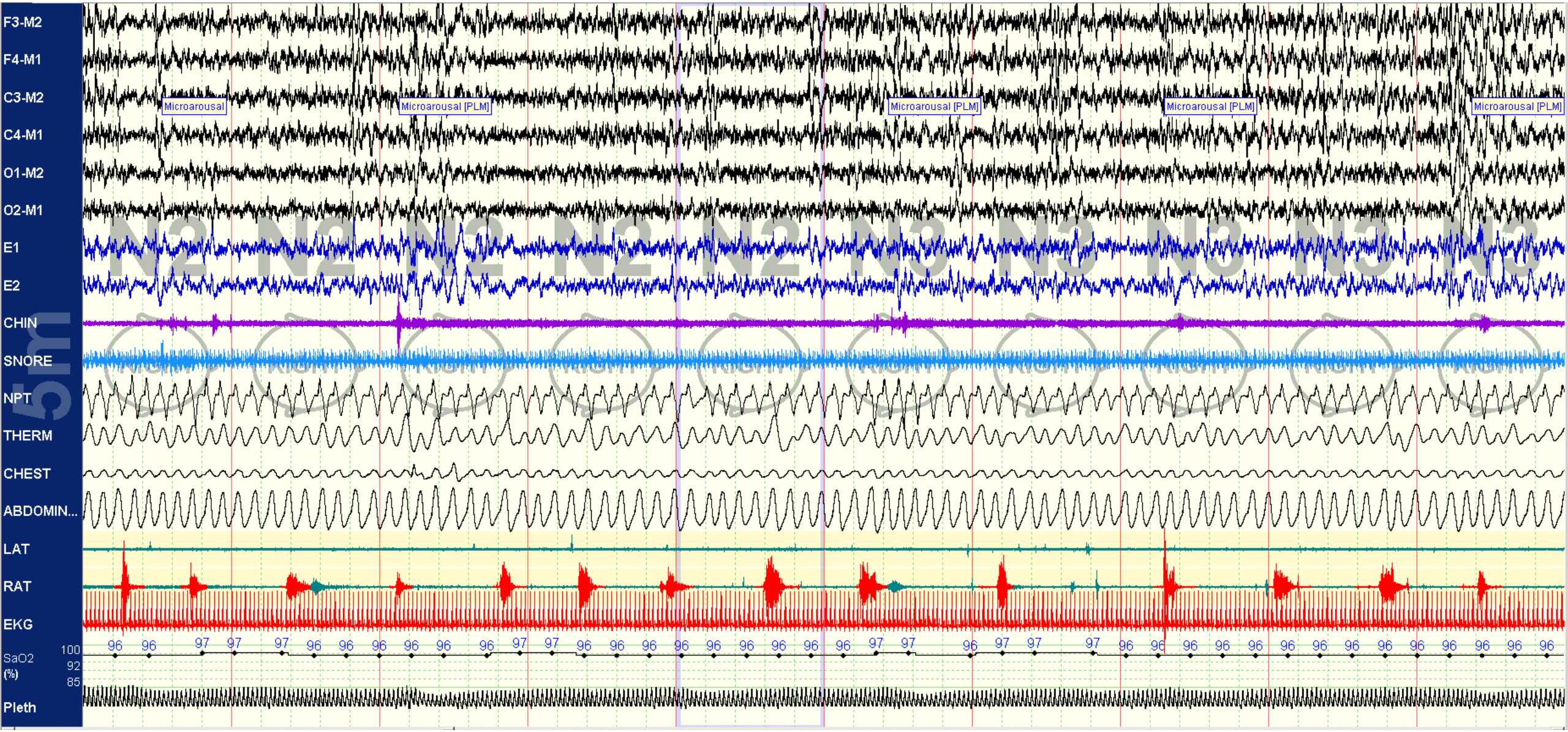

CAP periods
rich in delta bursts (A1) during the descending slope
or in arousals (A2 and A3) during the ascending slope
W
MT
REM
S1
S2
S3
S4
NCAP periods
rich in sleep spindles

CAP induced by PLMS

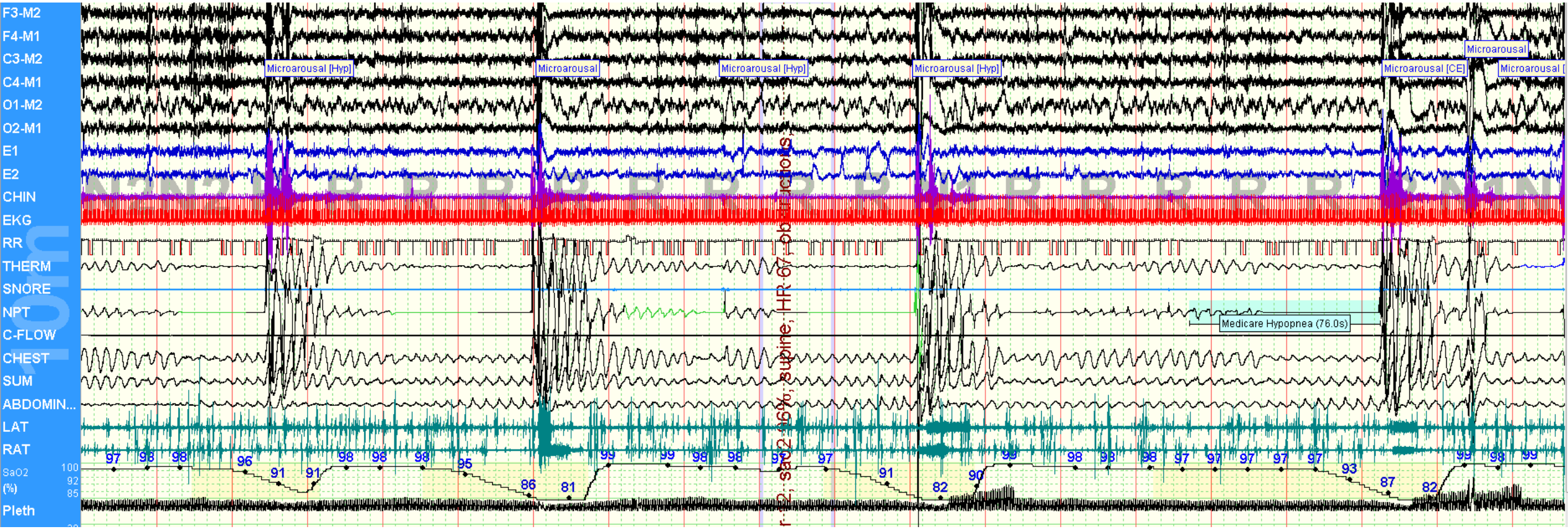


Alternating PLMS

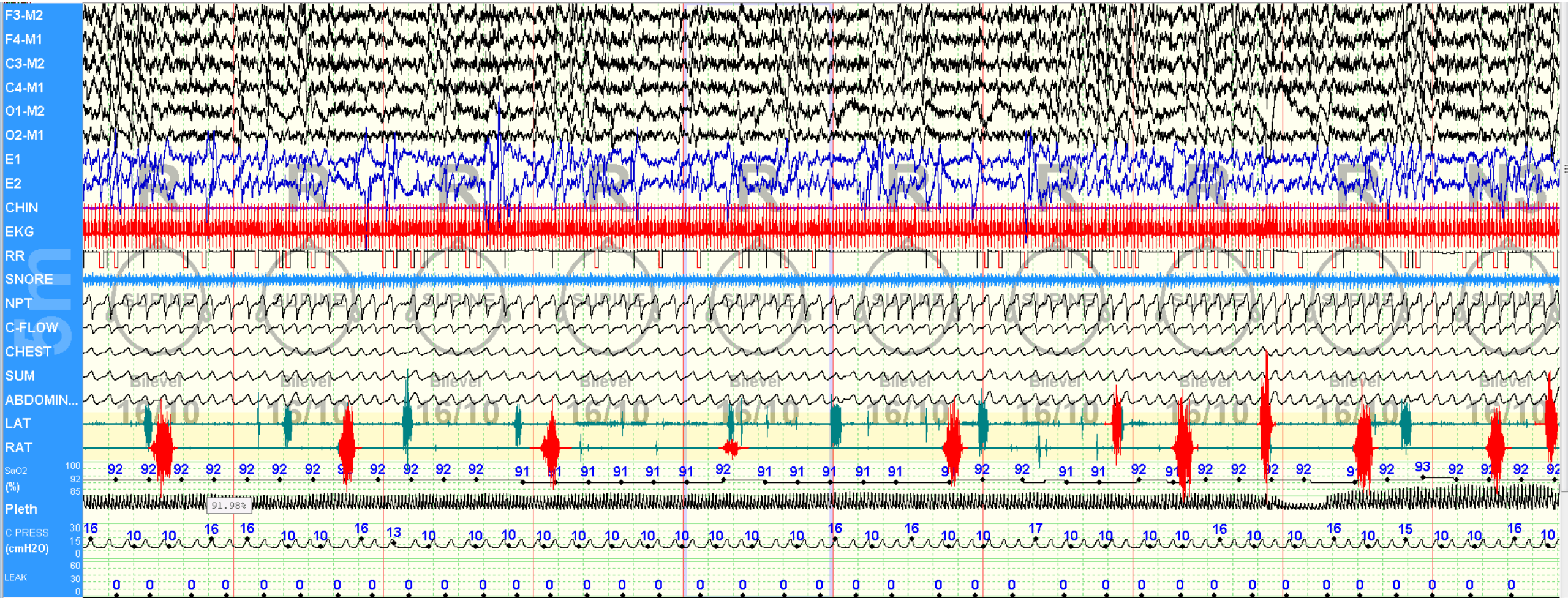


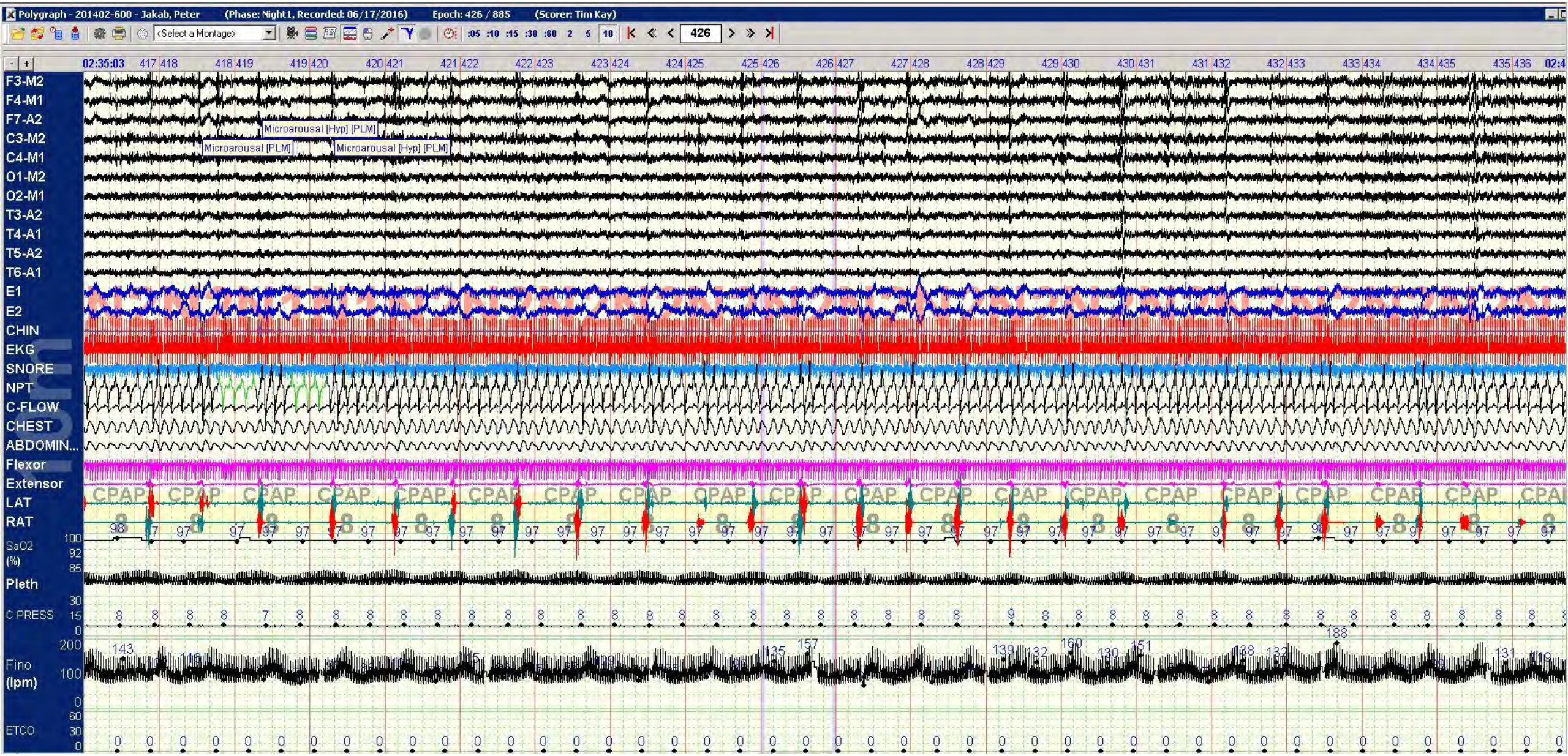

F3-M2
F4-M1
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
SNORE
NPT
THERM
CHEST
ABDOMIN...
LAT
RAT
EKG
SaO2 (%)
Pleth
Microarousal
Microarousal [PLM]
Microarousal [PLM]
Microarousal [PLM]
Microarousal [PLM]
N2 N2 N2 N2 N2 N3 N3 N3 N3
100
92
85
96 96 97 97 97 96 96 96 96 96 96 97 97 96 96 96 96 96 96 96 96 97 97 96 97 97 97 96 96 96 96 96 96 96 96 96 96 96 96 96

REM with respiratory events

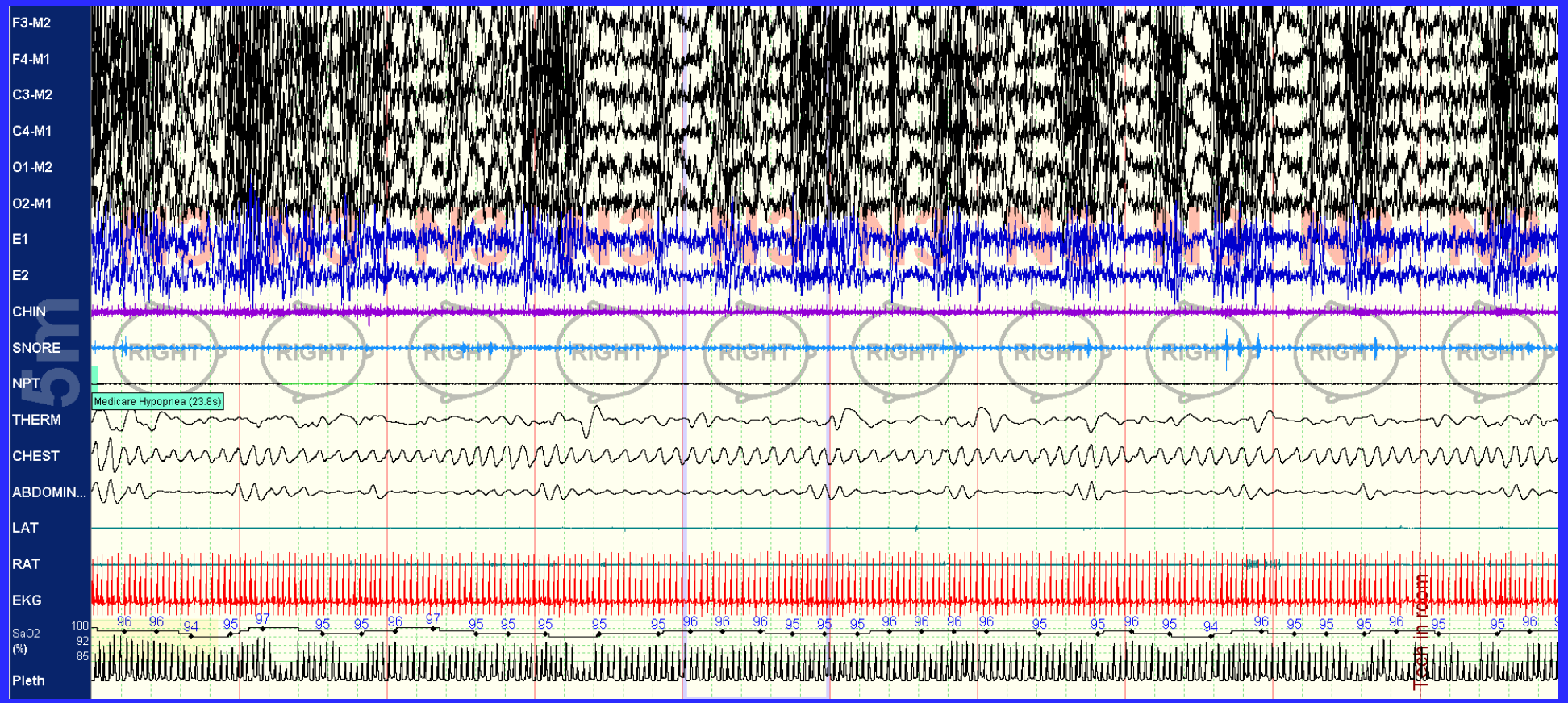


PLMS REM sleep

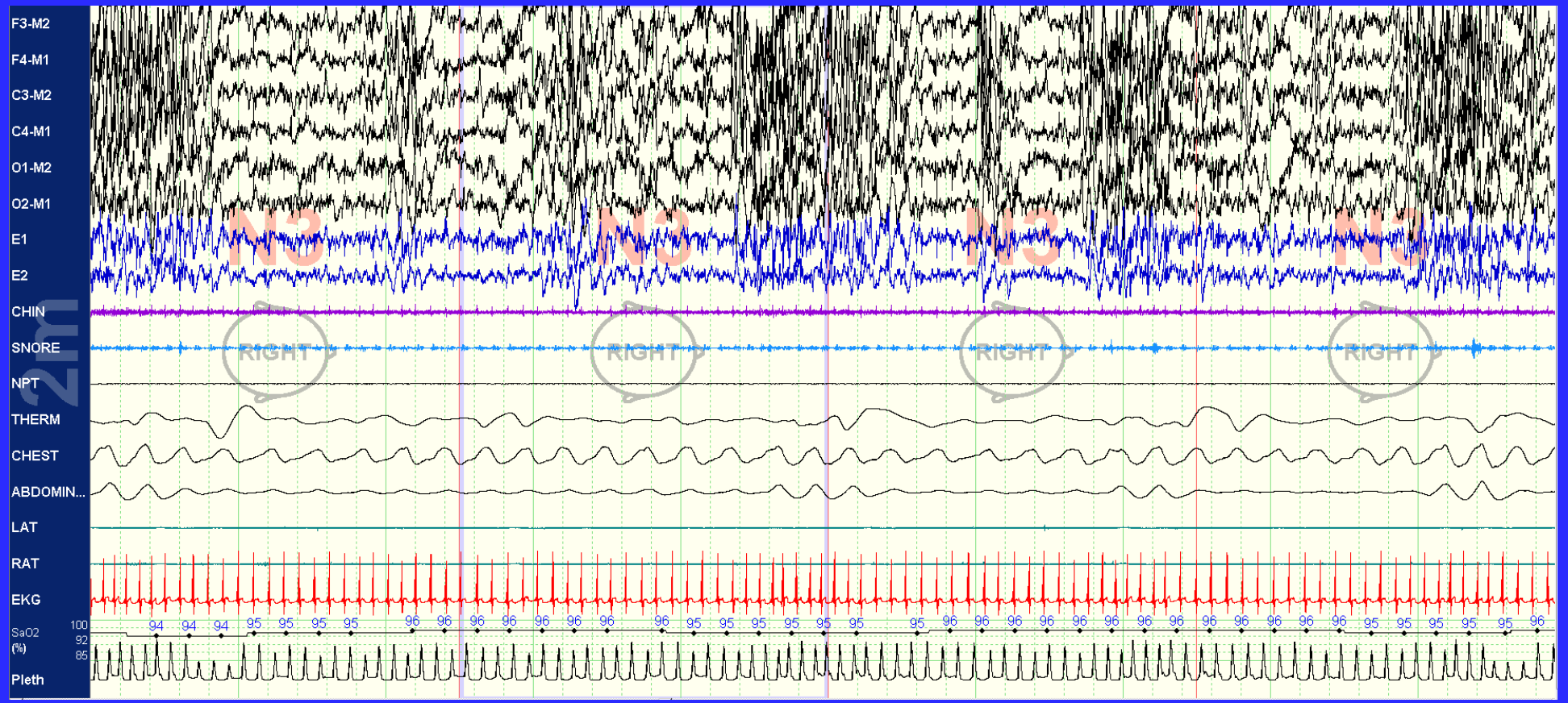



Polygraph - 201402-600 - Jakab, Peter (Phase: Night1, Recorded: 06/17/2016) Epoch: 426 / 885 (Scorer: Tim Kay)
<Select a Montage>
426
02:35:03
F3-M2
F4-M1
F7-A2
C3-M2
C4-M1
O1-M2
O2-M1
T3-A2
T4-A1
T5-A2
T6-A1
E1
E2
CHIN
EKG
SNORE
NPT
C-FLOW
CHEST
ABDOMIN...
Flexor
Extensor
LAT
RAT
SaO2 (%)
Pleth
C PRESS
Fino (lpm)
ETCO
Microarousal [Hyp] [PLM]
Microarousal [PLM]
Microarousal [Hyp] [PLM]
CPAP

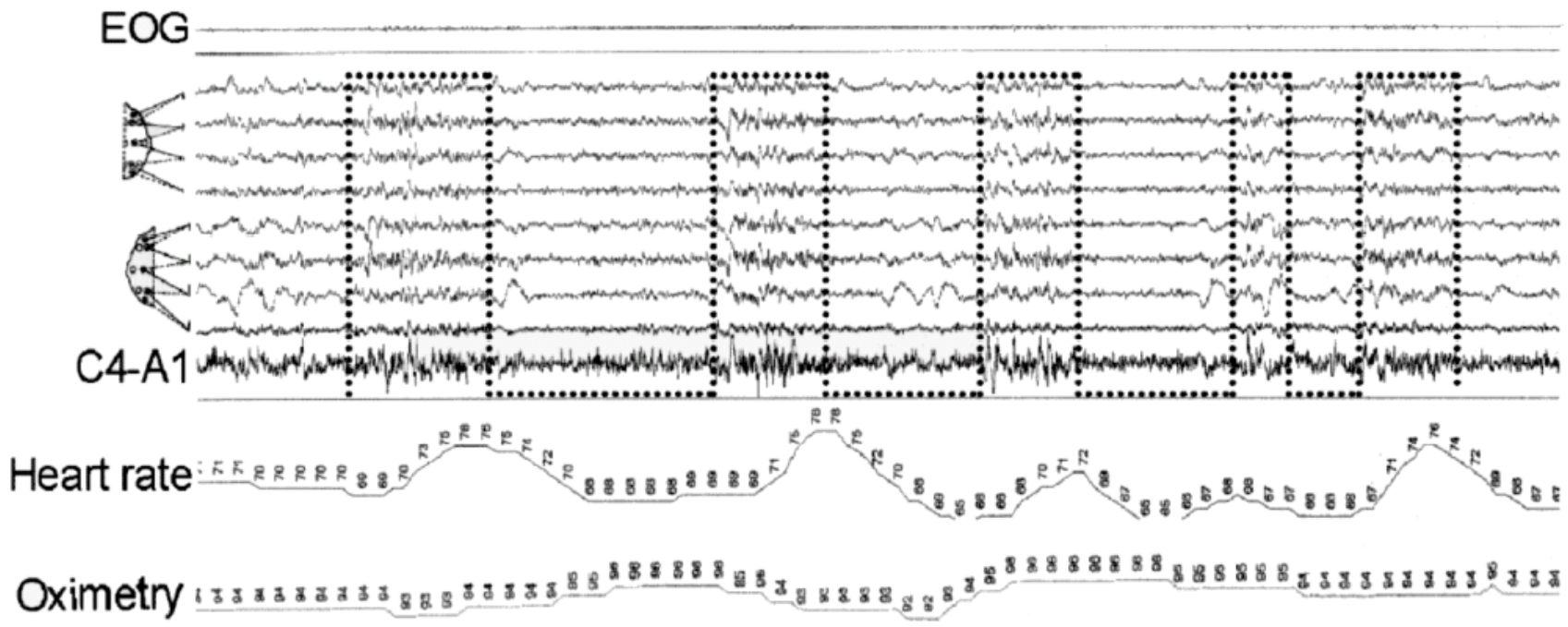
N3 CAP (5-minute)



N2 CAP (2-minute)

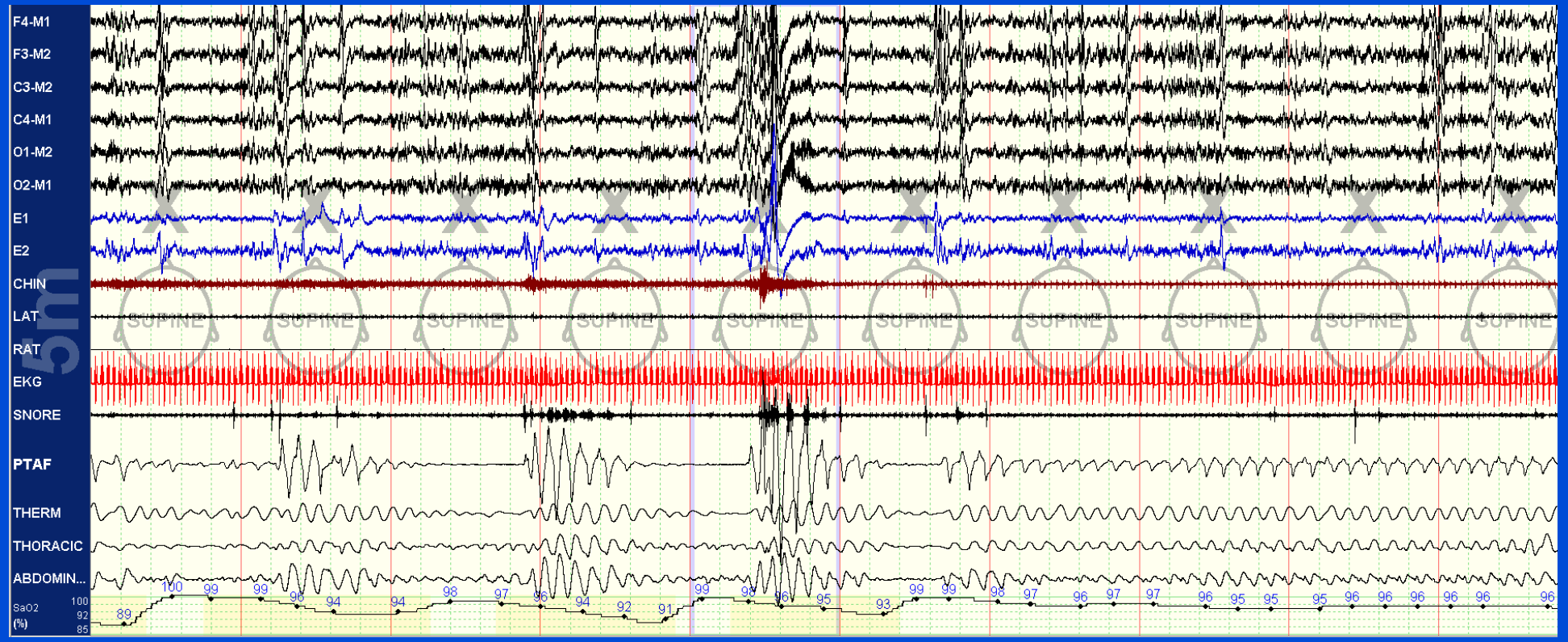


EEG and ECG and linked

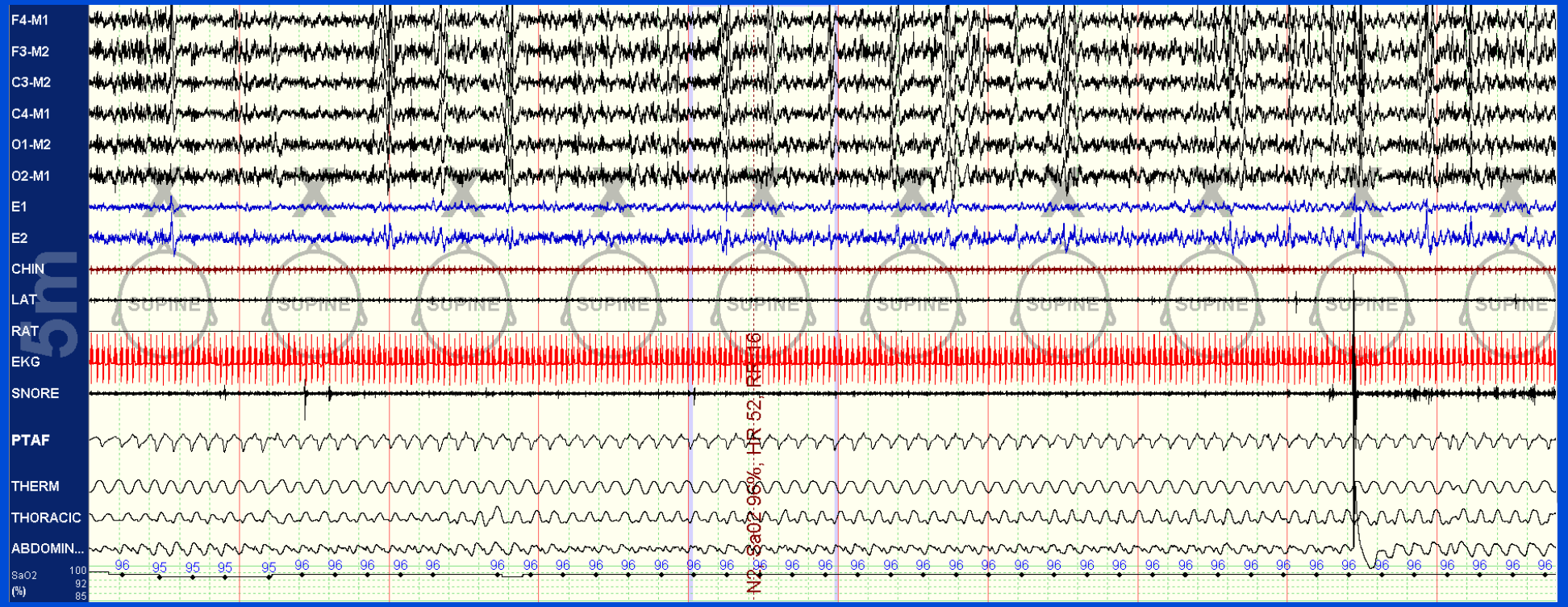


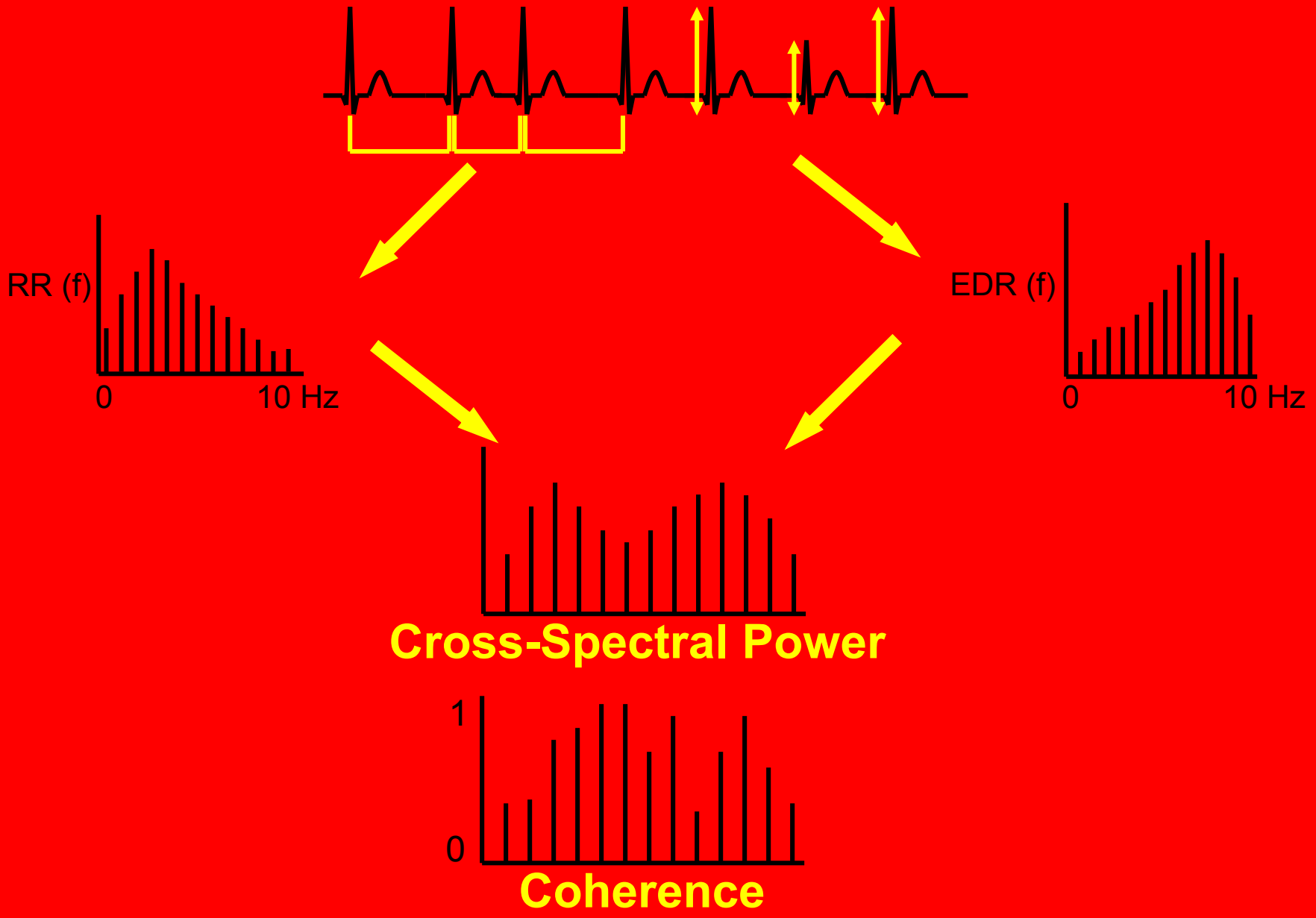
Unstable NREM

Transition to Unstable



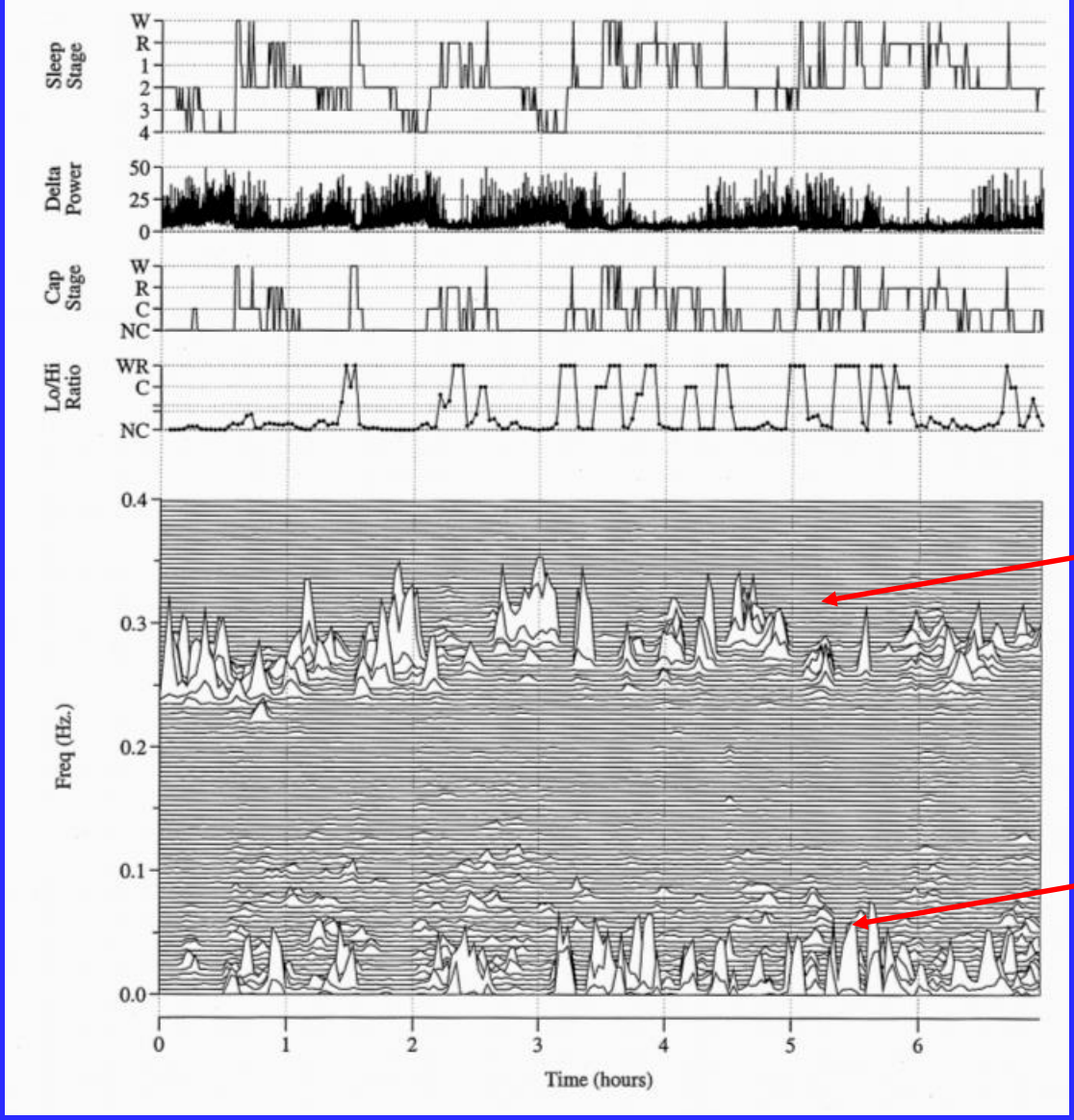
Stable NREM


F4-M1
F3-M2
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
LAT
RAT
EKG
SNORE
PTAF
THERM
THORACIC
ABDOMIN...
SaO2 (%)
100
92
85
SUPINE
N2 SaO2 96%, HR 52, RR 16



Cardiopulmonary Coupling =
[Cross-Spectral Power]^2 X [Coherence]

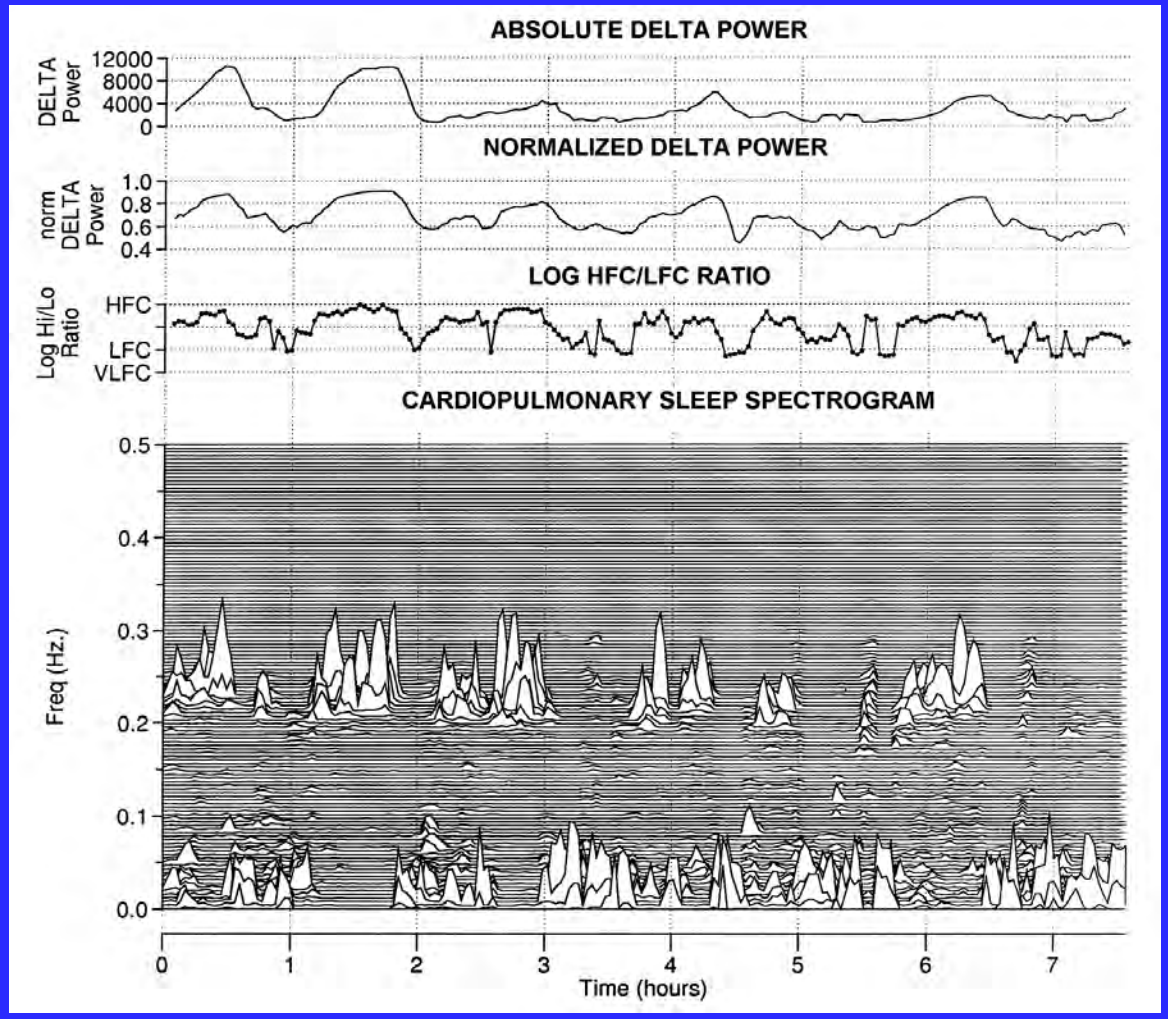
Sleep spectrogram in health



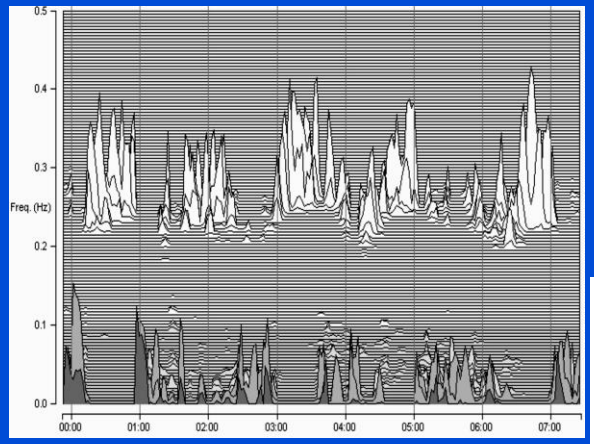
High-frequency coupling

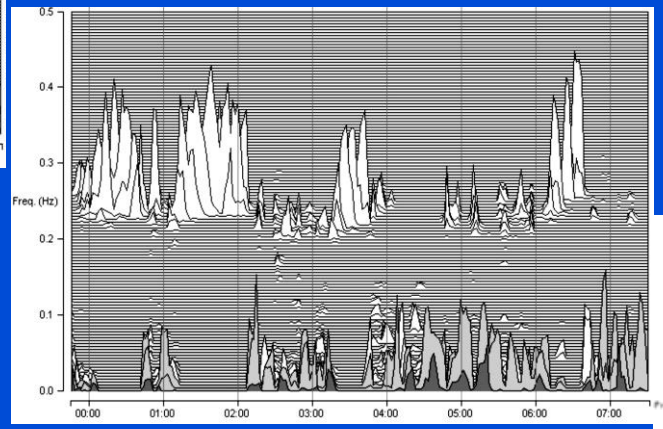
Low-frequency coupling

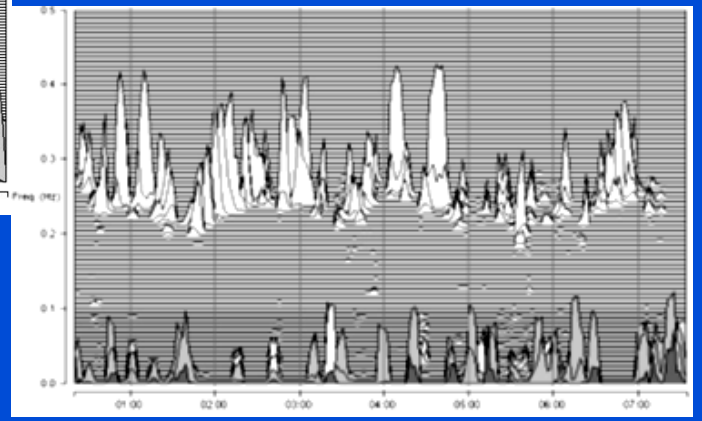
Slow wave power and ECG-spectrogram

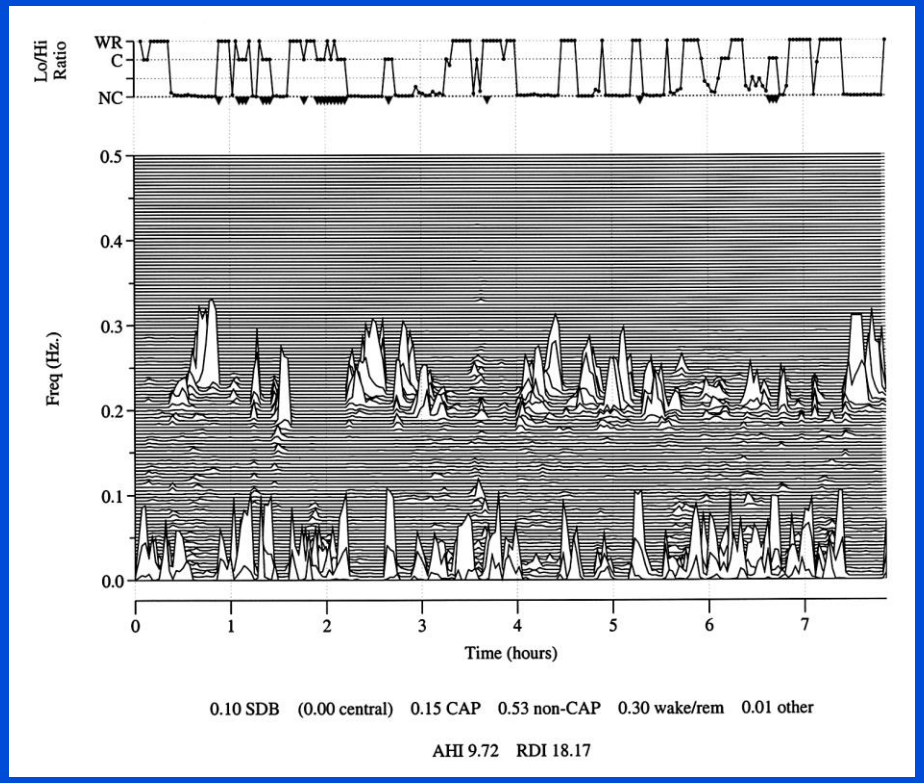


Night-to-night stability



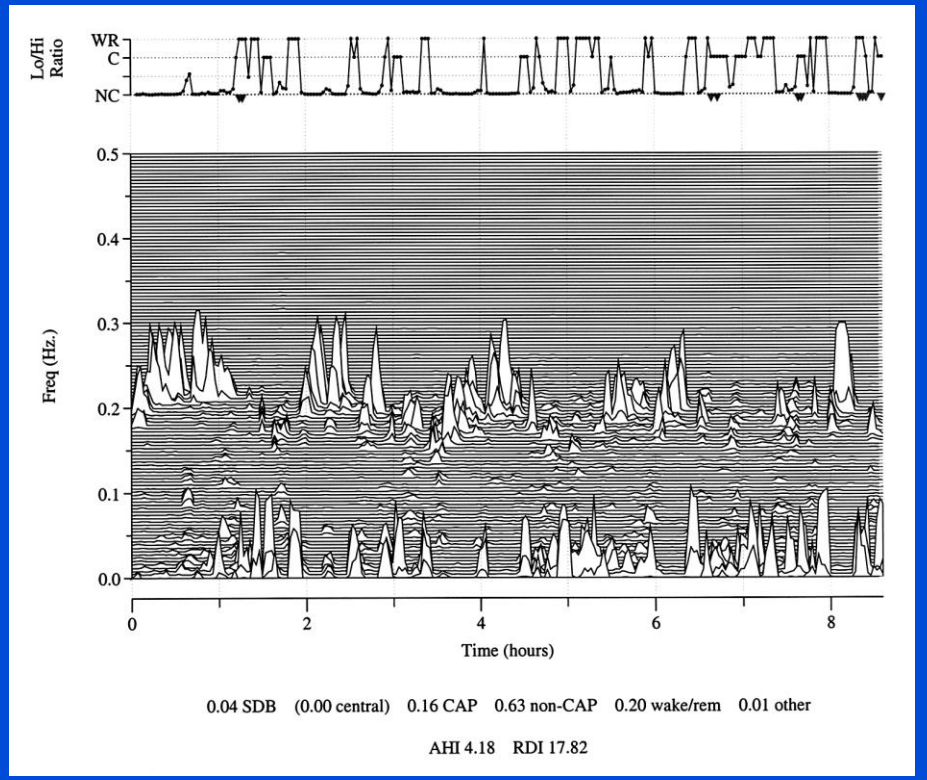




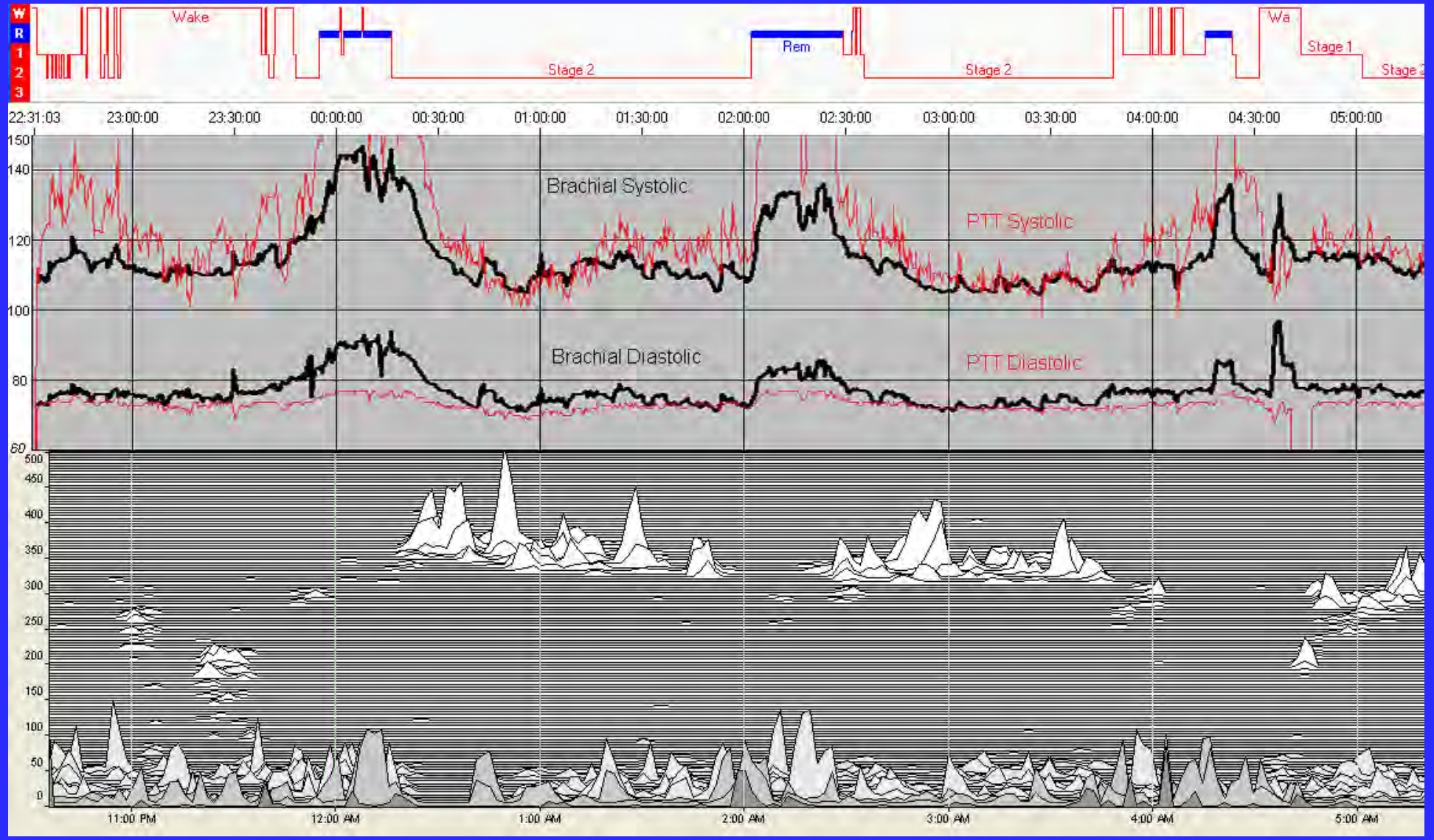


Rested - human

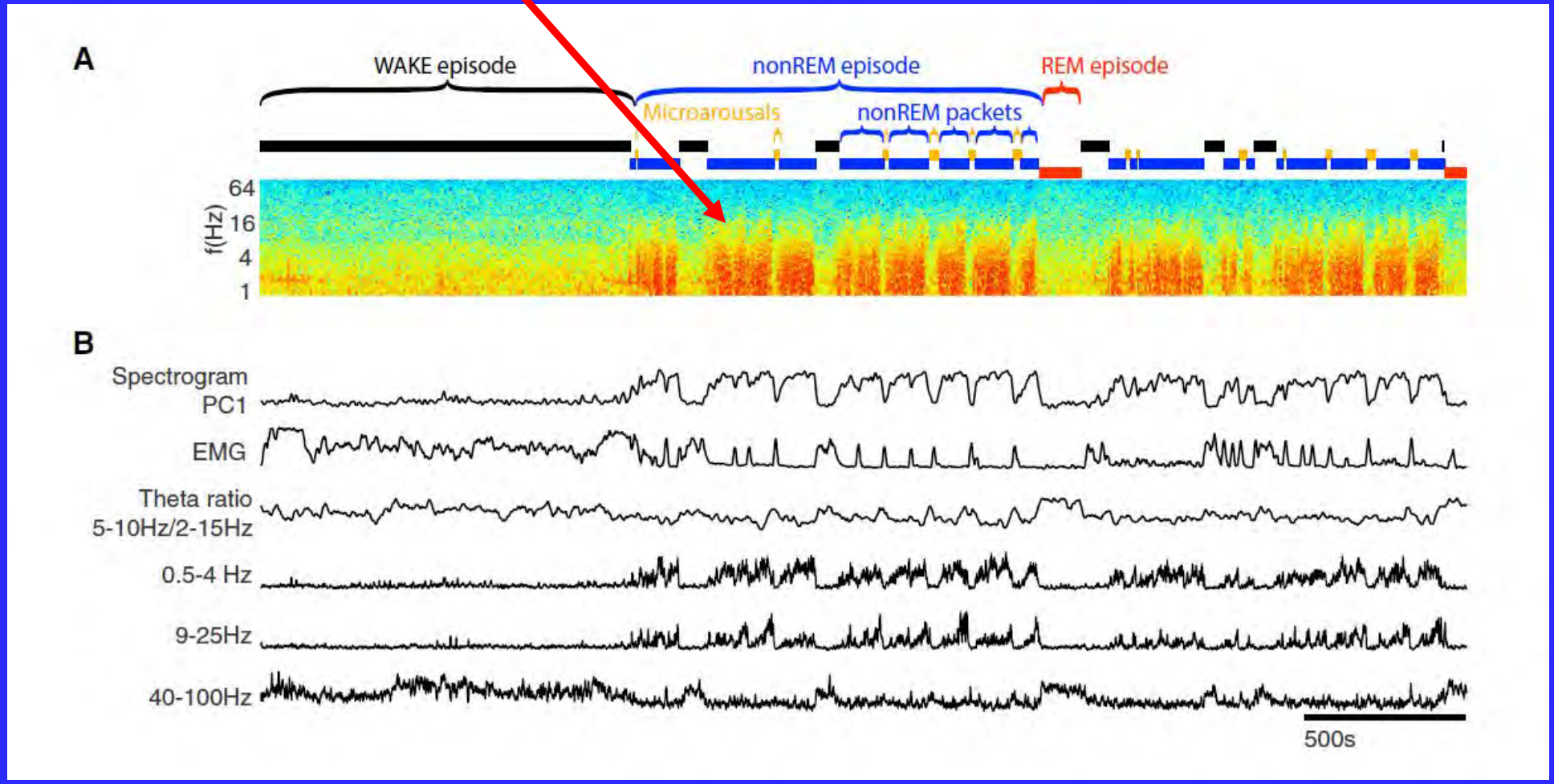
Sleep deprivation recovery – increased HFC all across the night



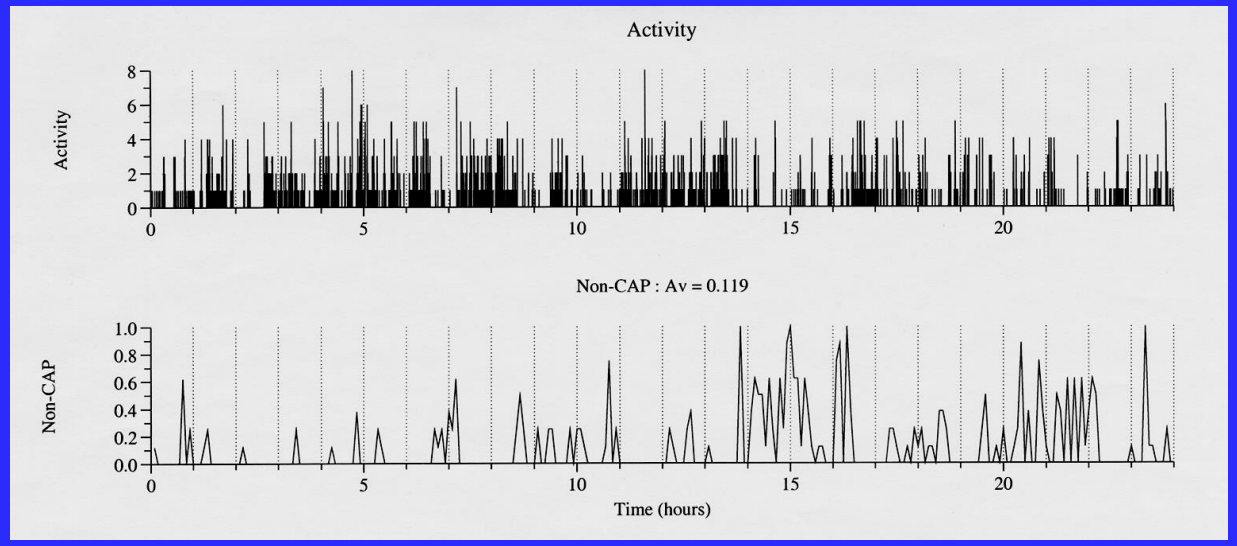
Blood pressure “dips” only during the periods of high frequency coupling



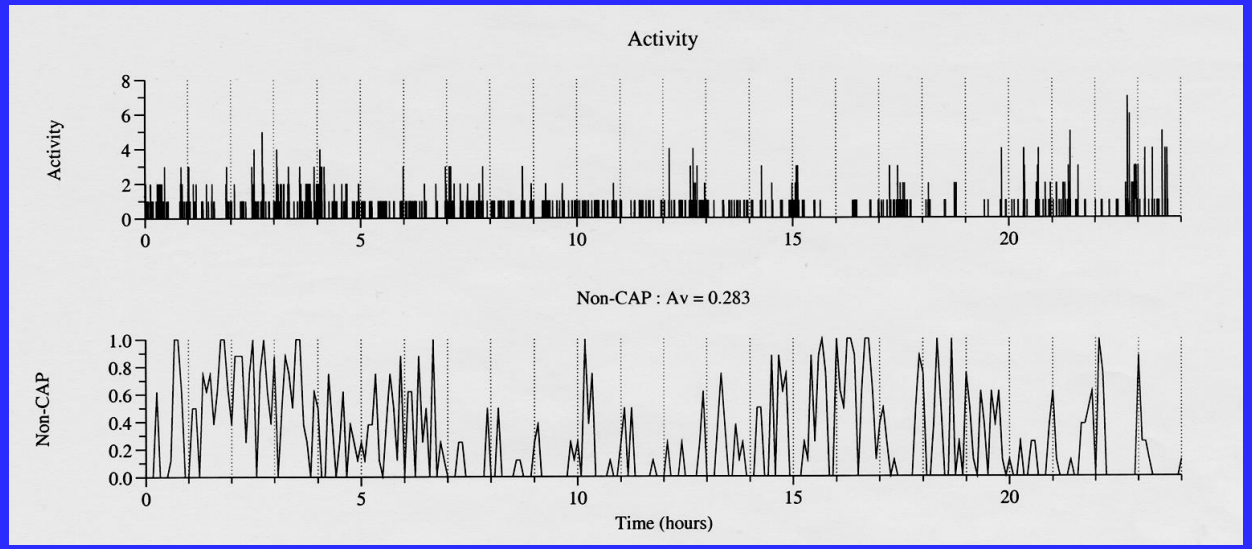
Direct recording from the cortex of rodents show that NREM occurs in “packets”



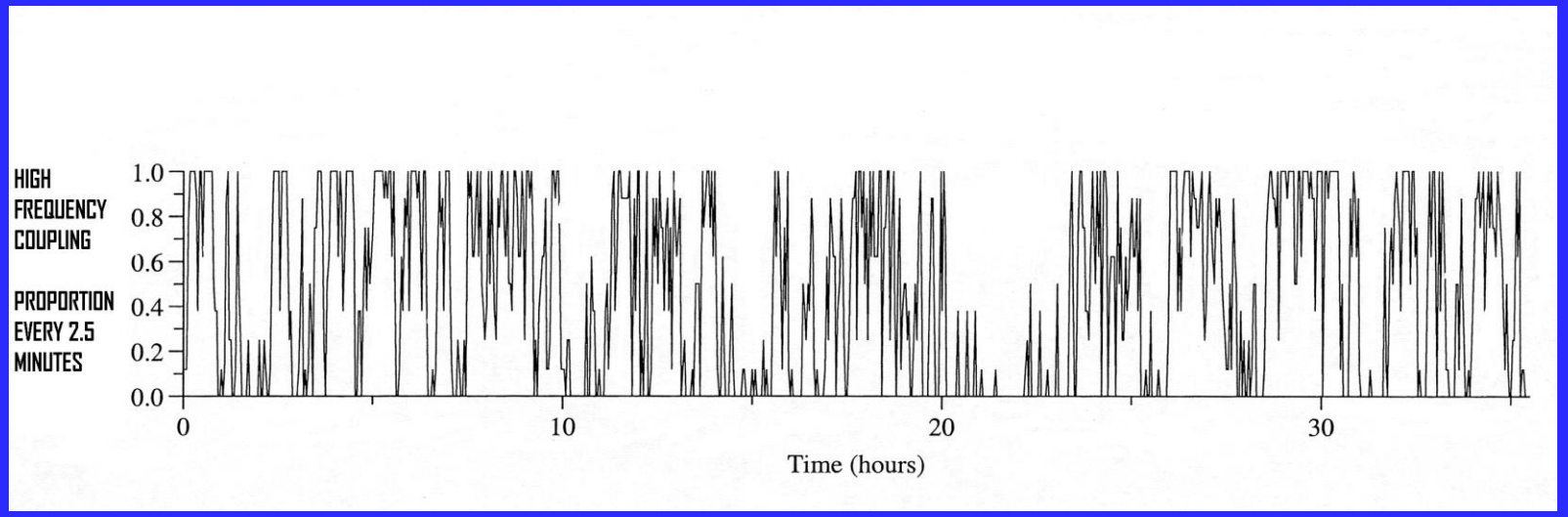
Benzodiazepines decrease slow wave but increases integrated stability (rat data)

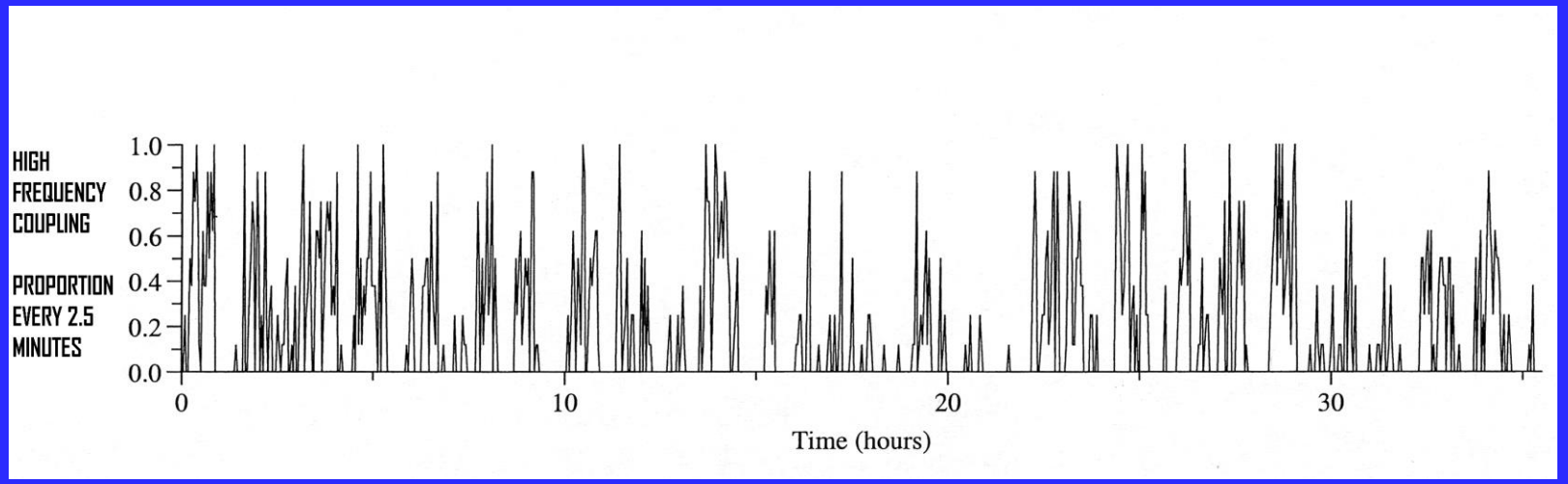


Lorazepam 0.9 mg/Kg/day

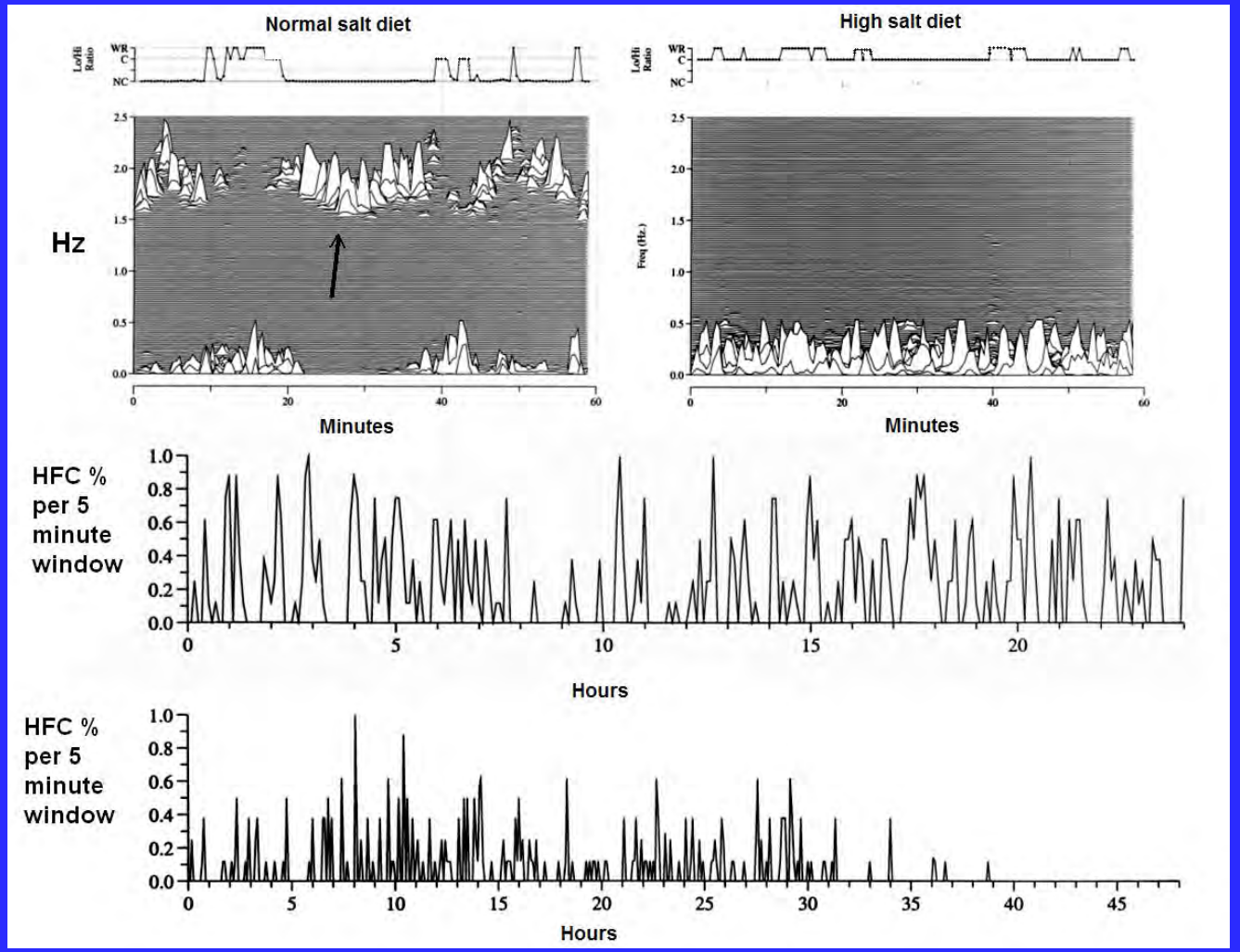


Sleep fragmentation in Alzheimer's disease (transgenic mouse)





Sleep network fragmentation in heart failure



A speculative word on idiopathic hypersomnia

- Relevant to all hypersomnias with substantial sleep inertia
- A network transition disorder
- Pathological persistence of sleep network = long sleep
- Pathological inability to switch off for wake network = sleep inertia
- Mixed sleep-wake network persistence = fog
- Stimulants do not work well due to persistent activation of components of the NREM sleep network

Stabilizing networks to target sleep disorders

- Sleep restriction - redistribution of homeostatic sleep drive, improved network continuity, interactions, connectivity, increased TDS
- Sodium oxybate – improve network cohesion and sharpen state boundaries
- Acetazolamide – stabilize respiratory control network
- Benzodiazepines – stabilize integrated sleep network
- Stimulants – stabilize wake network and sleep-wake boundaries
- RBD circuit – REM behavior disorder
- Closed loop stimulation approach to enhance slow waves in NREM sleep

In summary

- Sleep is a unique networked state
- Multi-physiology
- Four dimensions
- Dynamic, morphing
- Phase transitions
- Predictable changes in disease
- Predictable effects of therapy
- Network analysis is severely underused in sleep research and non-existent in sleep practice