Sleep as a Network State (Part II)

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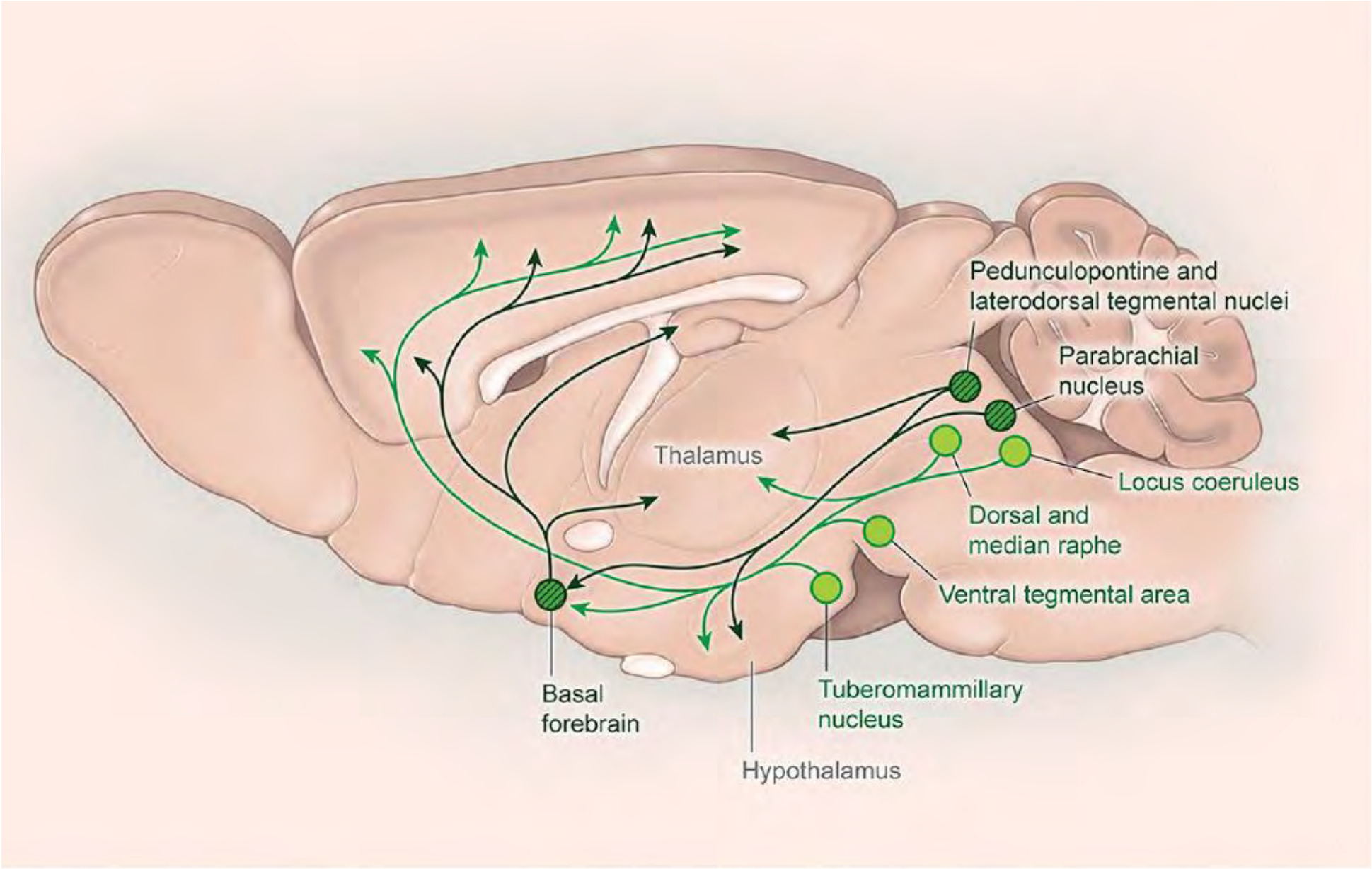
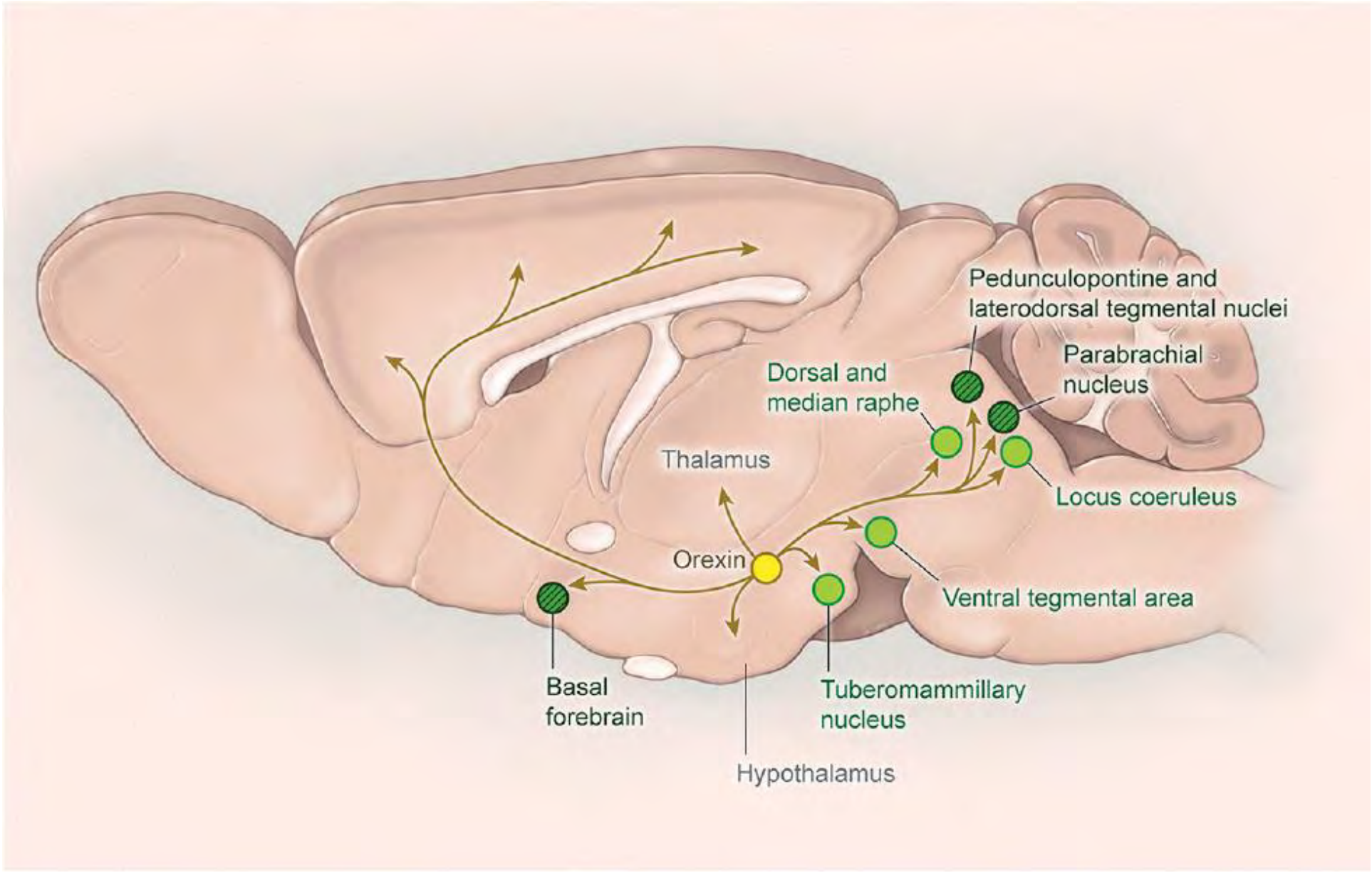
Wake

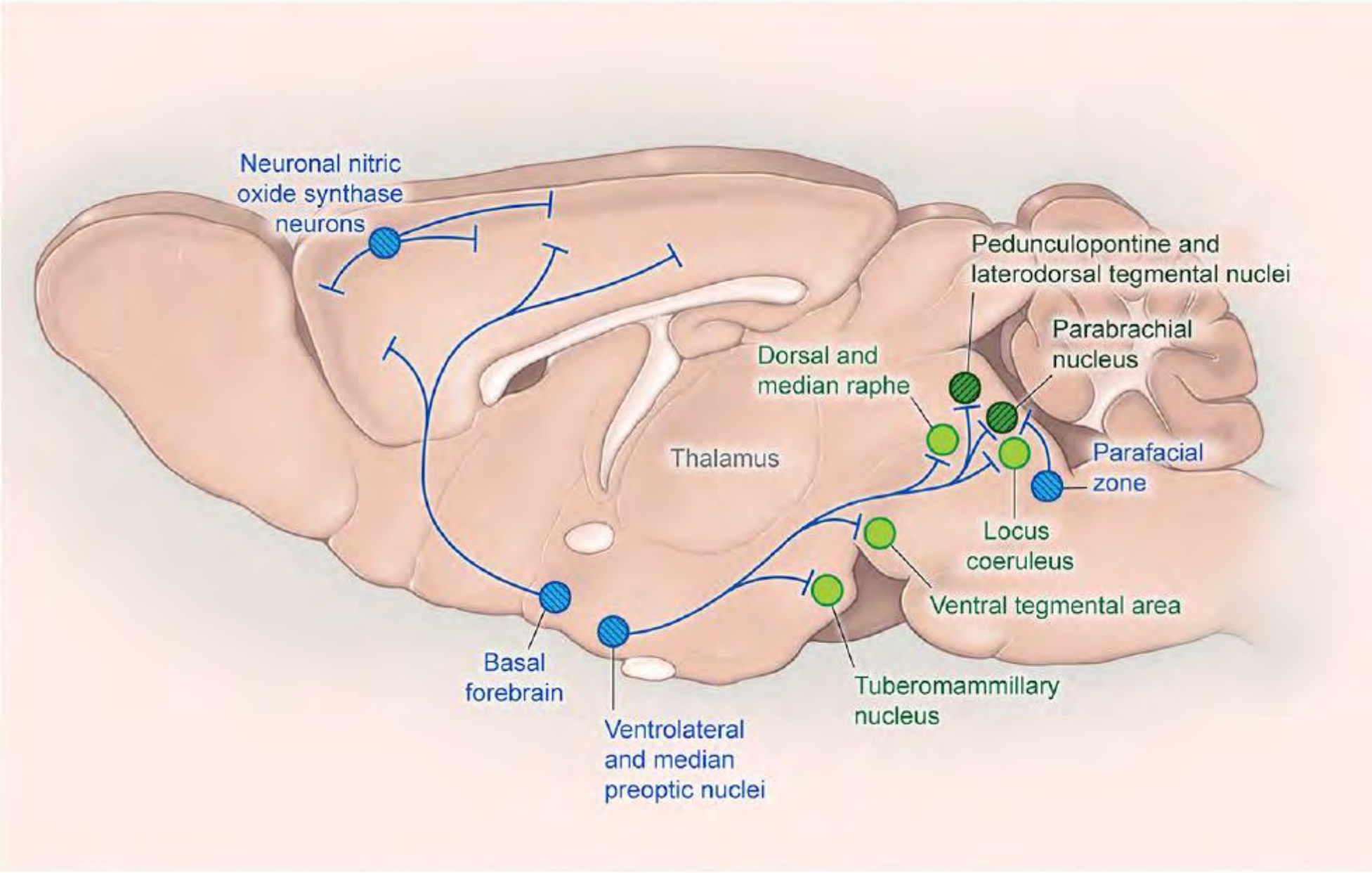
Neuron 201722;93: 747-765.



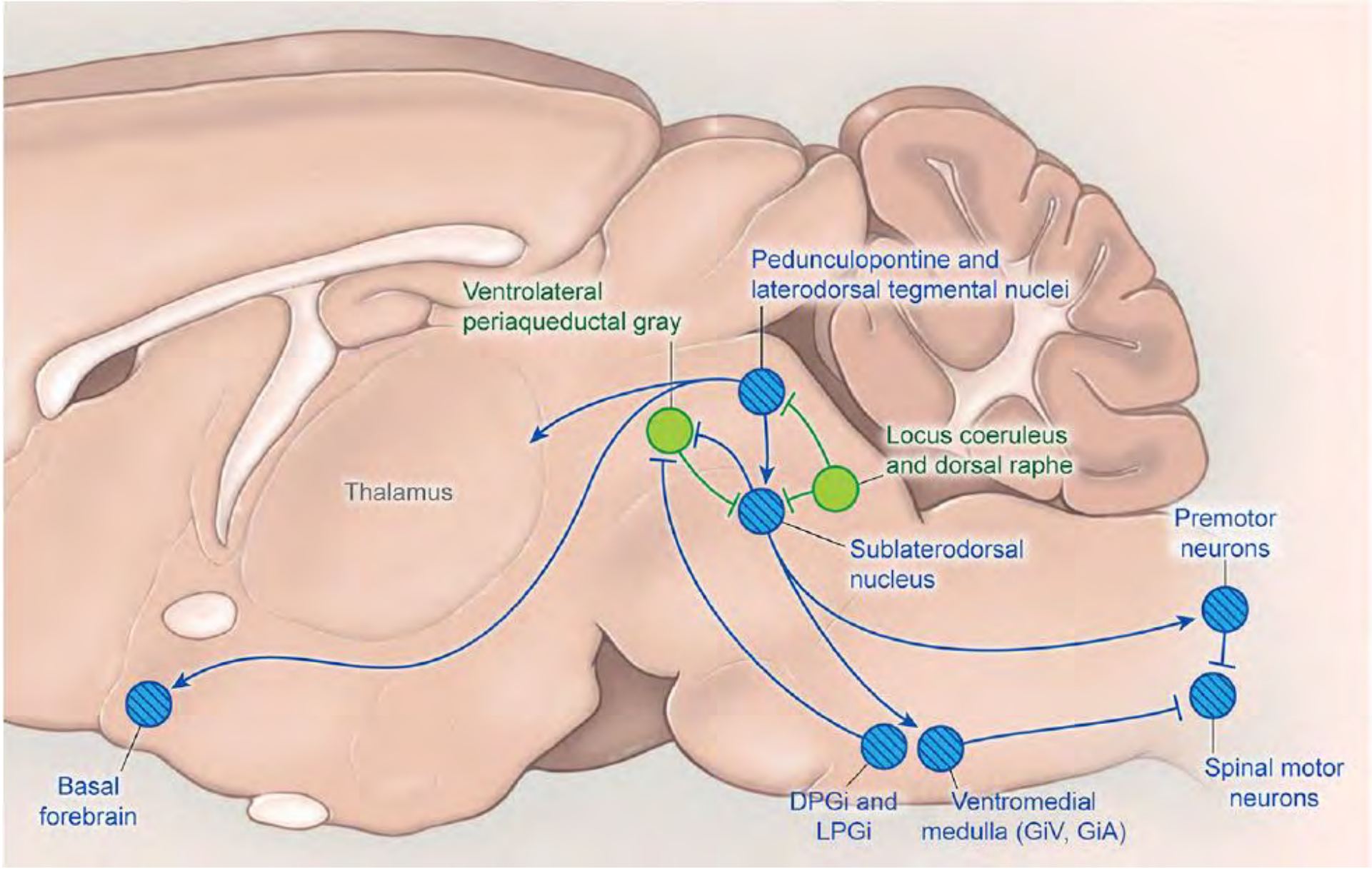
Orexin


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

Continuation….why bother? Targets

- Epilepsy – brain health, prognostic and therapeutic markers
- Dementia – progression, regression through cortical network
- Stroke recovery – brain-autonomic-cardiac-respiratory network
- Atrial fibrillation – recurrence risk through autonomic network
- Neuromuscular disorders – brain-muscle networks, targeted therapy
- Parkinson's disease brain-autonomic-motor network
- Dyspnea - cardiorespiratory-cortical network
- Sleep disorders
  - Sleep apnea impact on heart failure, atrial fibrillation
  - Periodic limb movements
  - Insomnia
  - Hypersomnia, narcolepsy

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?

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

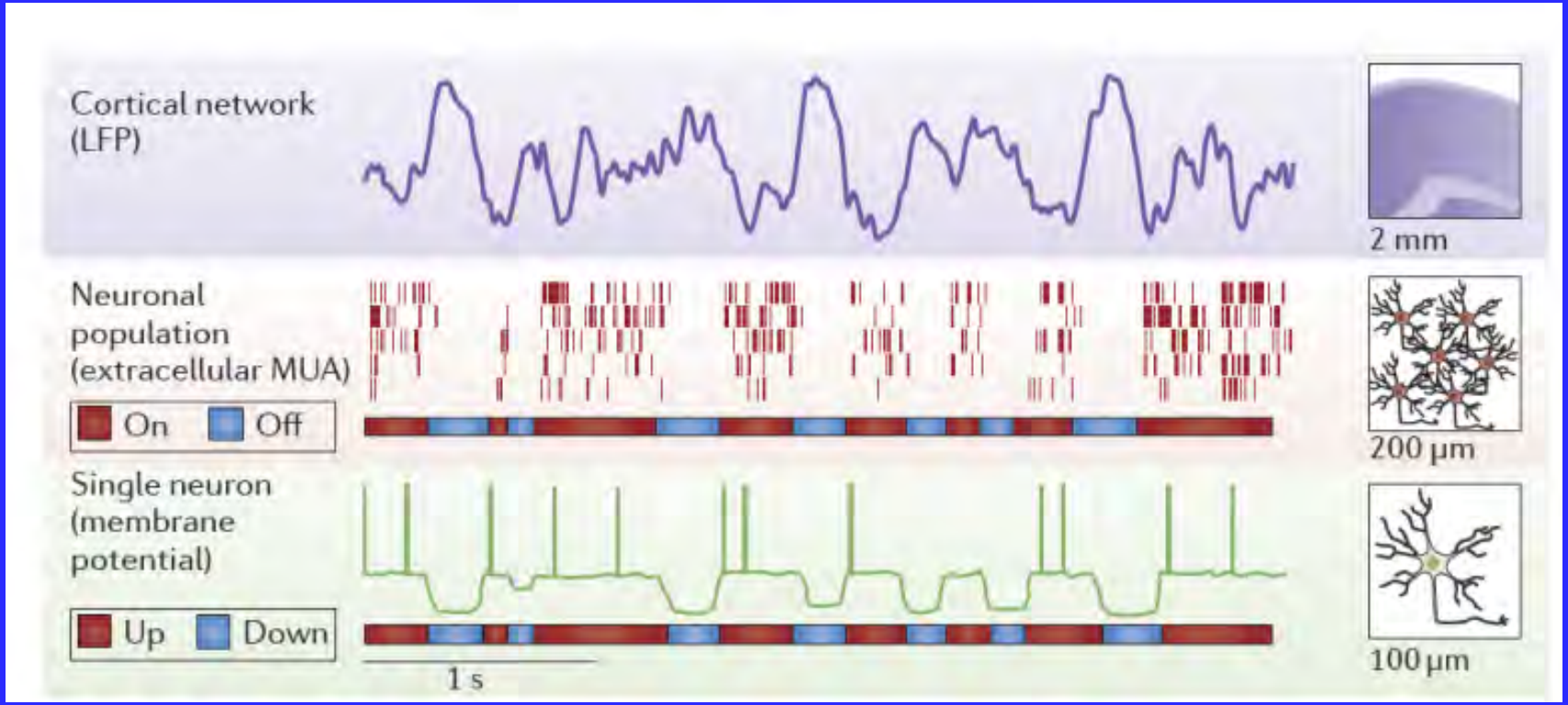
Network breakdown

- **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**

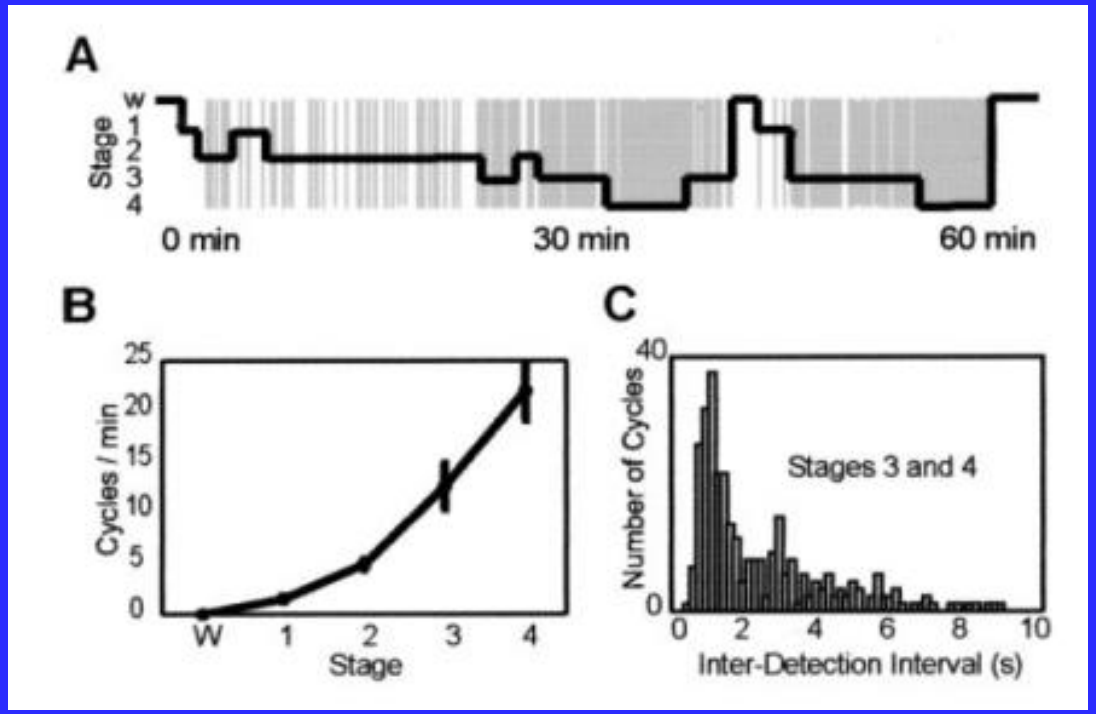
Network breakdown

- 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

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



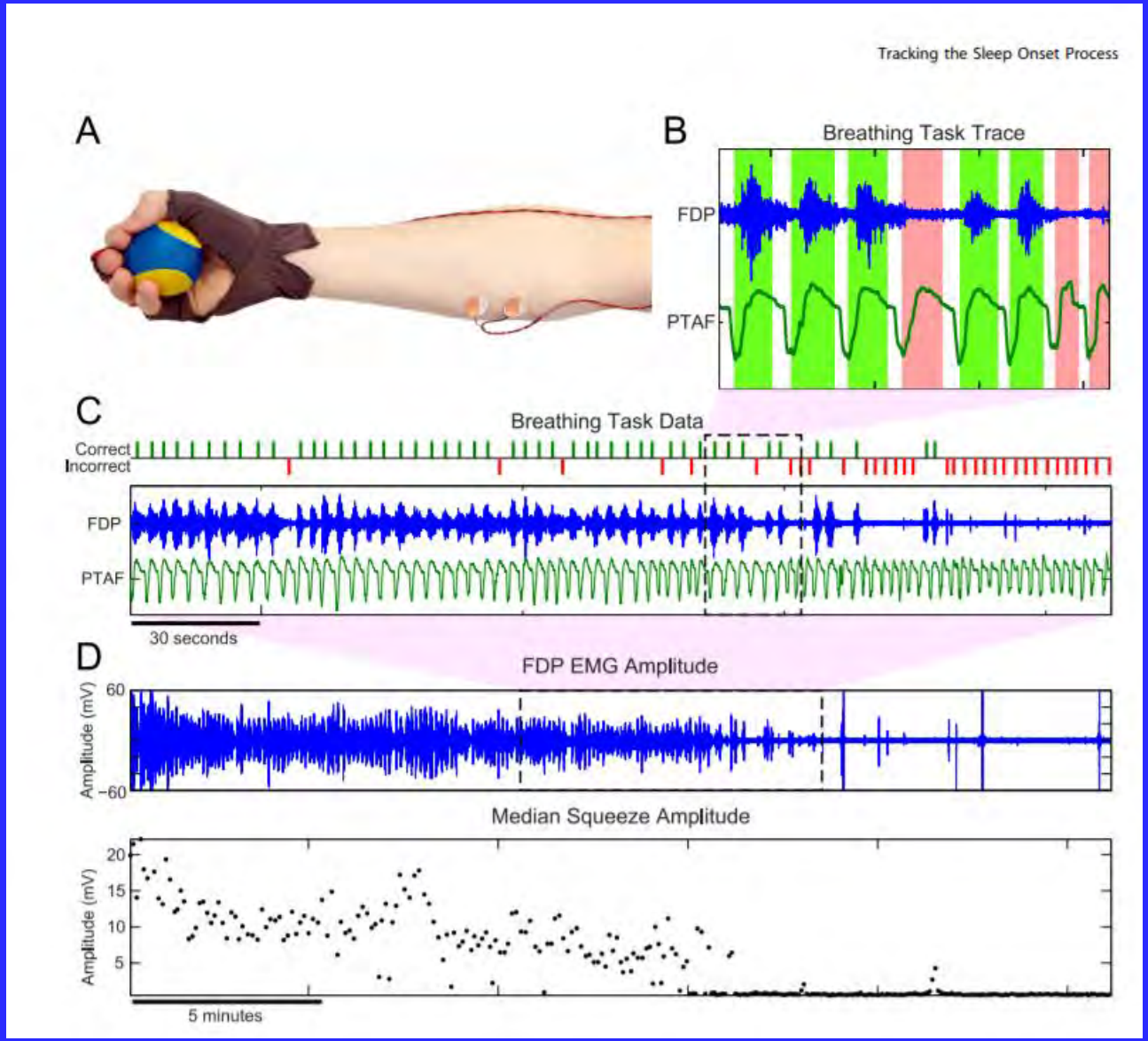
The Slow Oscillation (SO) builds in frequency and spatial extent as sleep starts and deepens. Below-high within individual stability.



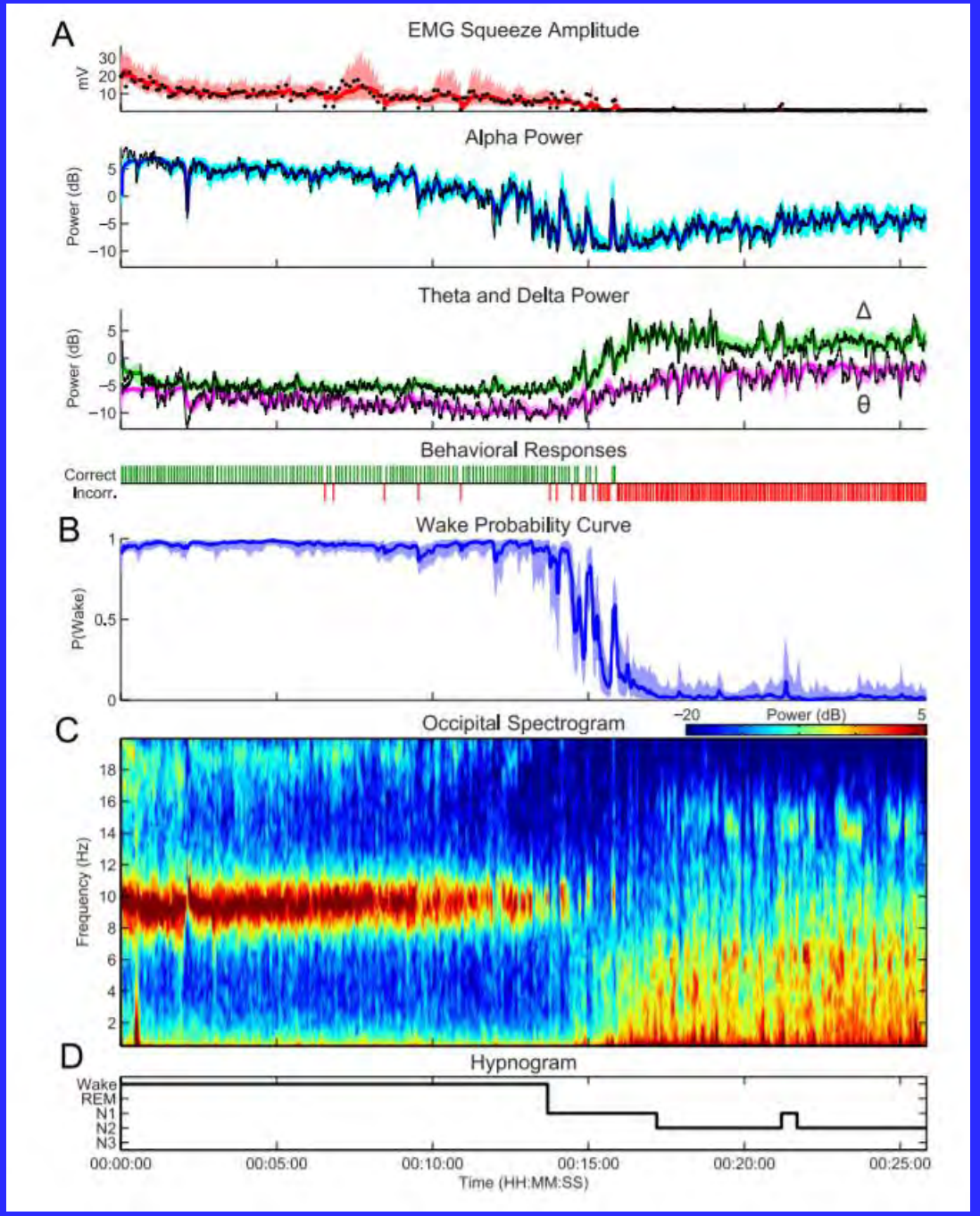
Consequences of the time of night distribution of the SO glue

- 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)

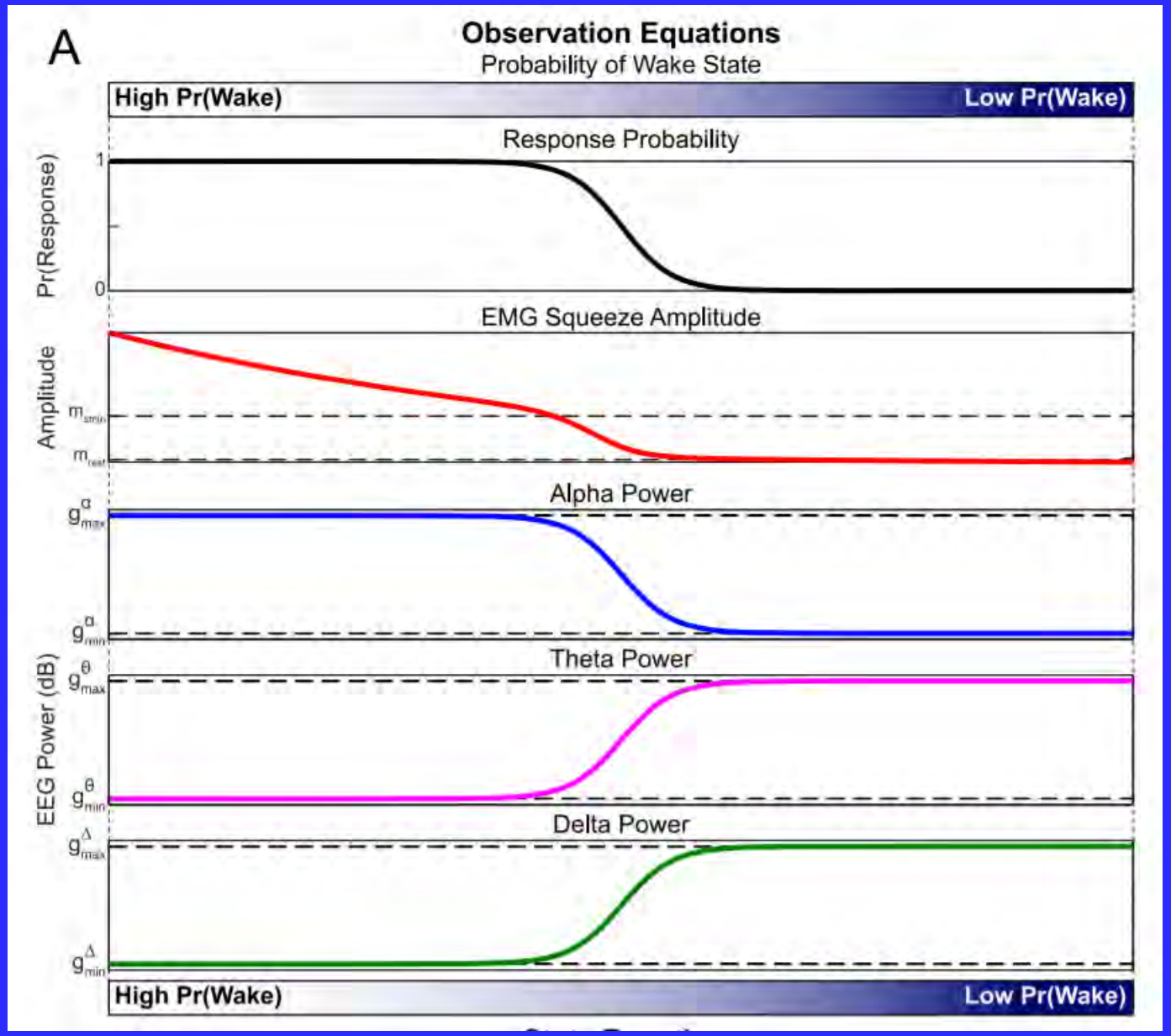
Sleep Onset


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

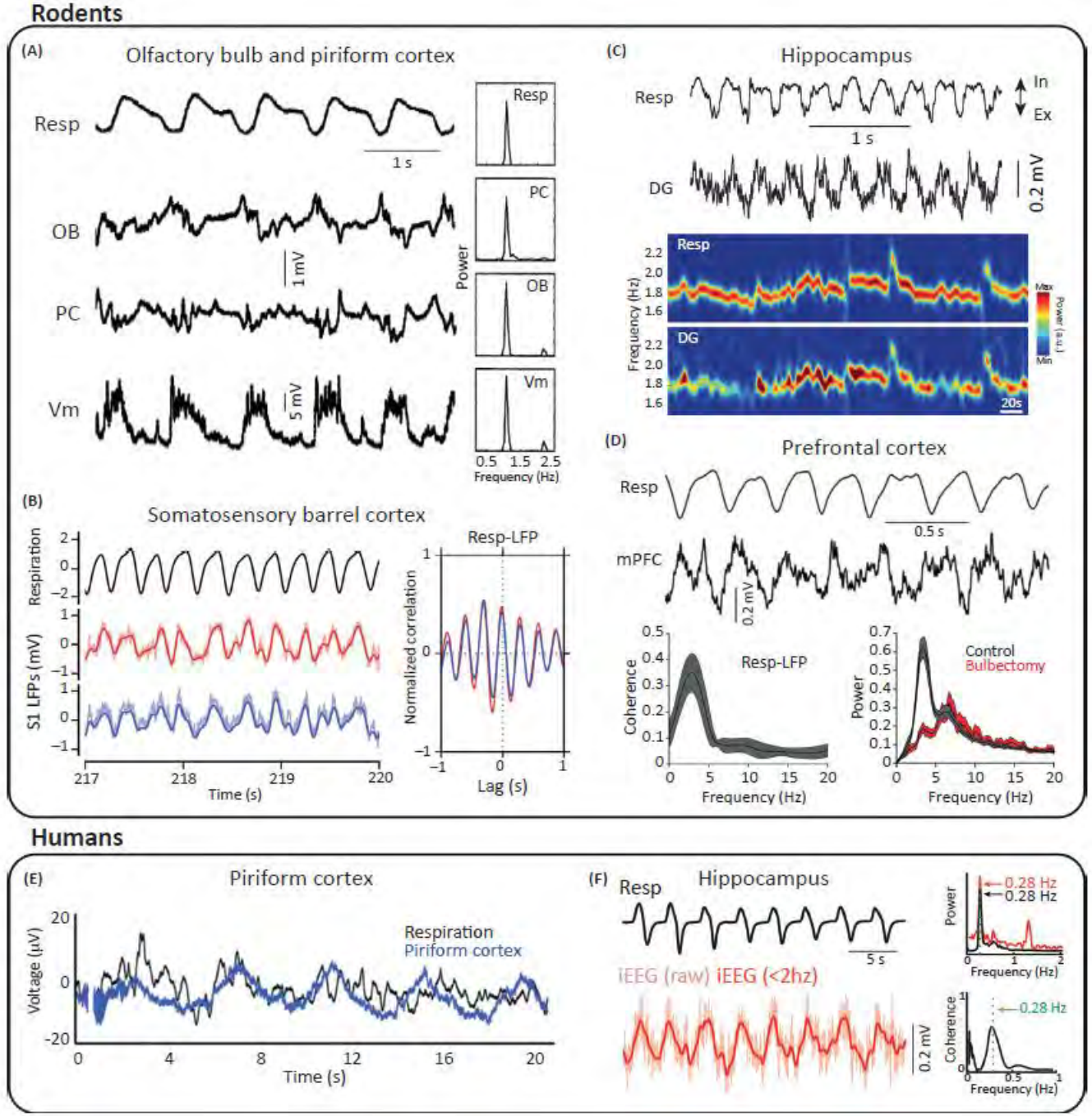
Sleep Onset


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)

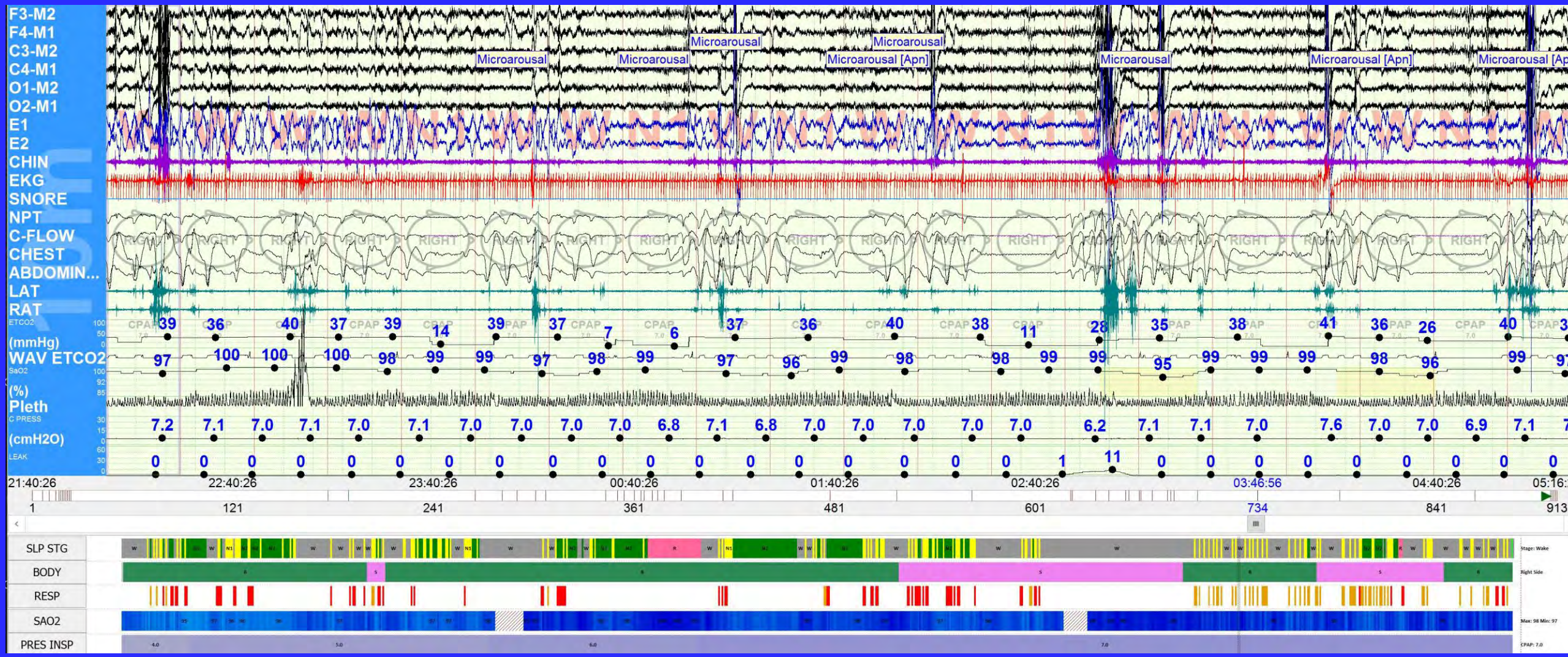
Sleep Onset


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)

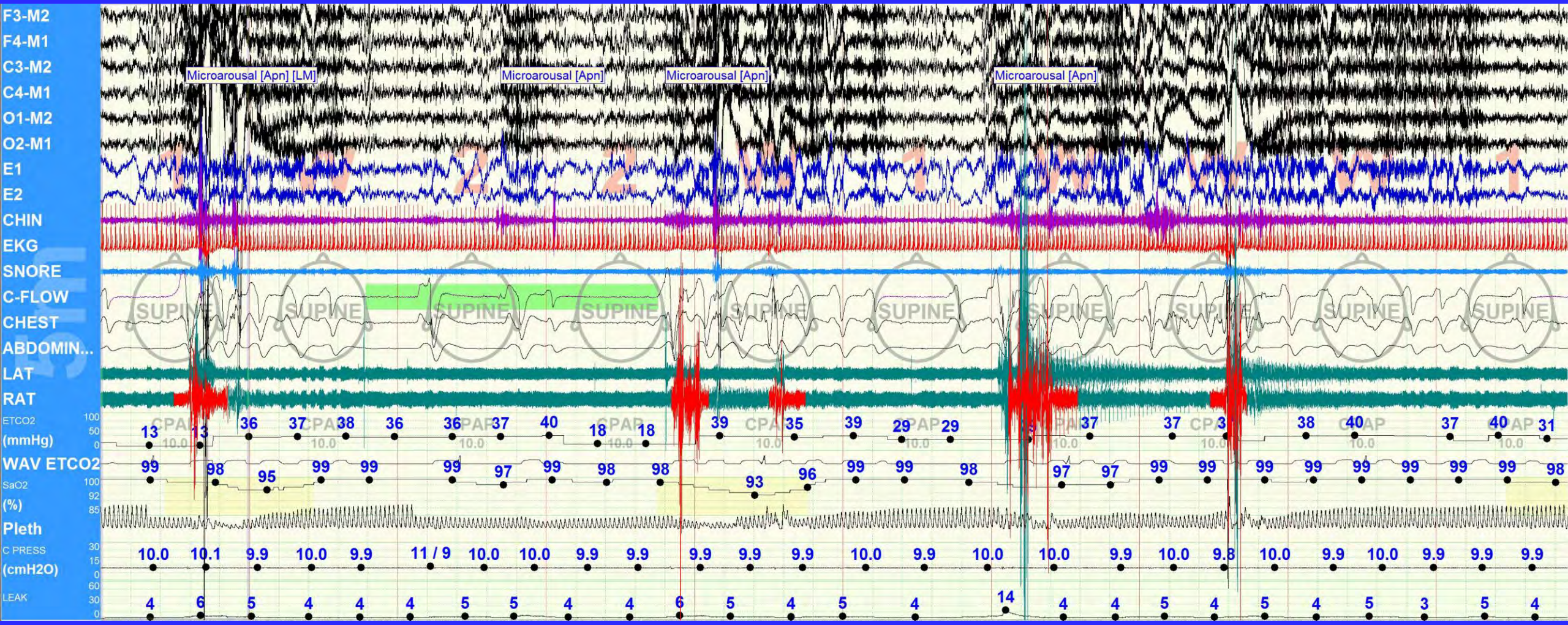
Respiration-Entrained Brain Rhythms Are Global but Often Overlooked.
Trend Neurosci 2018;41:186-197.



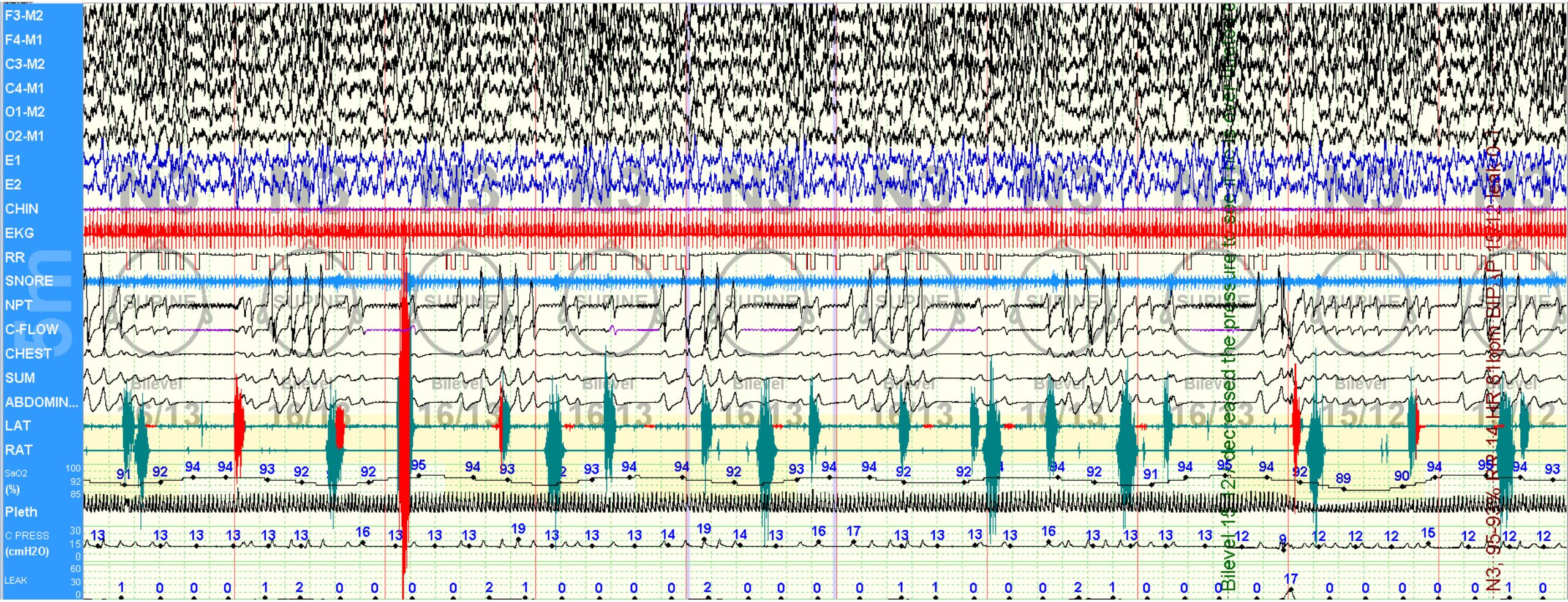
Amplified wake-sleep transitional instability (AWSTI)

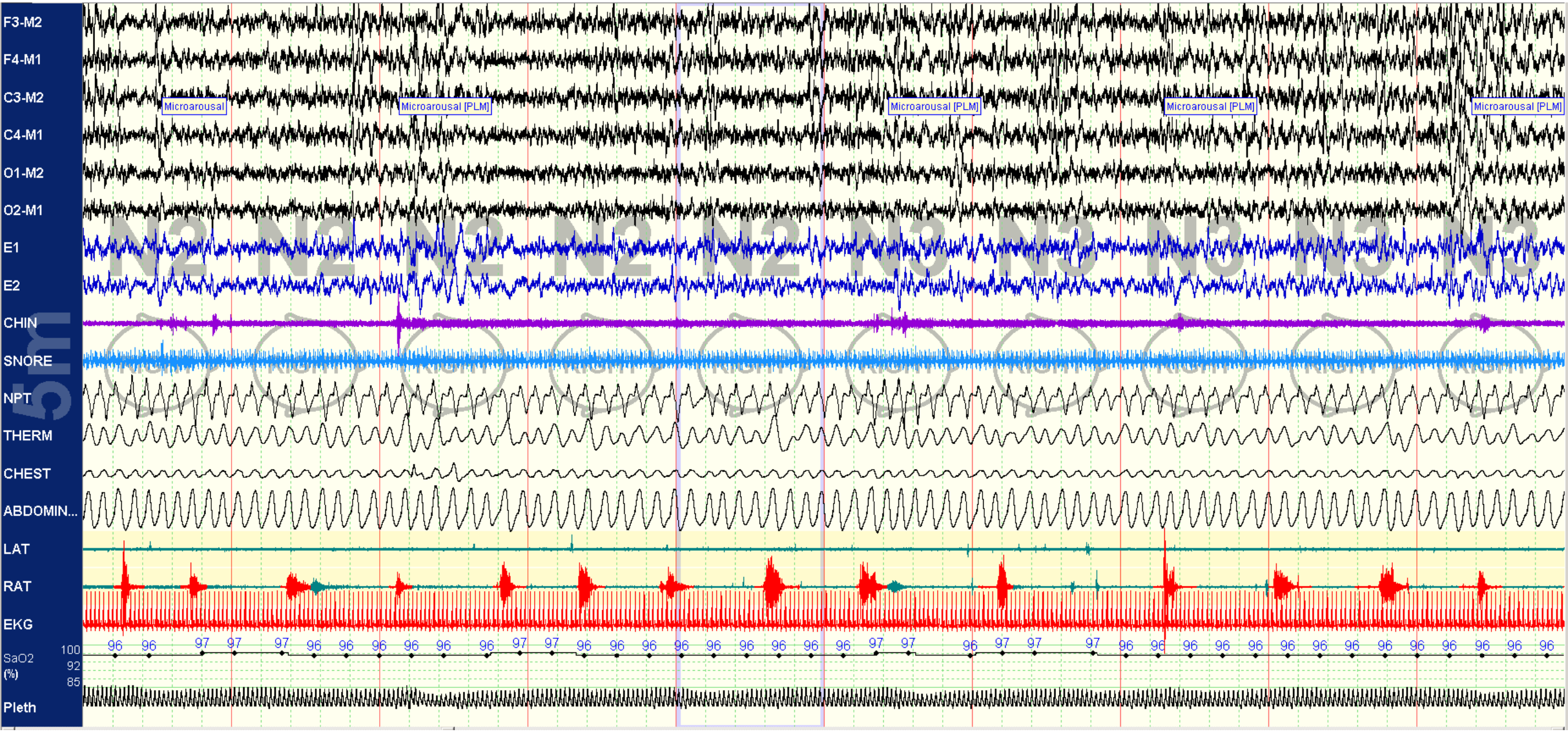


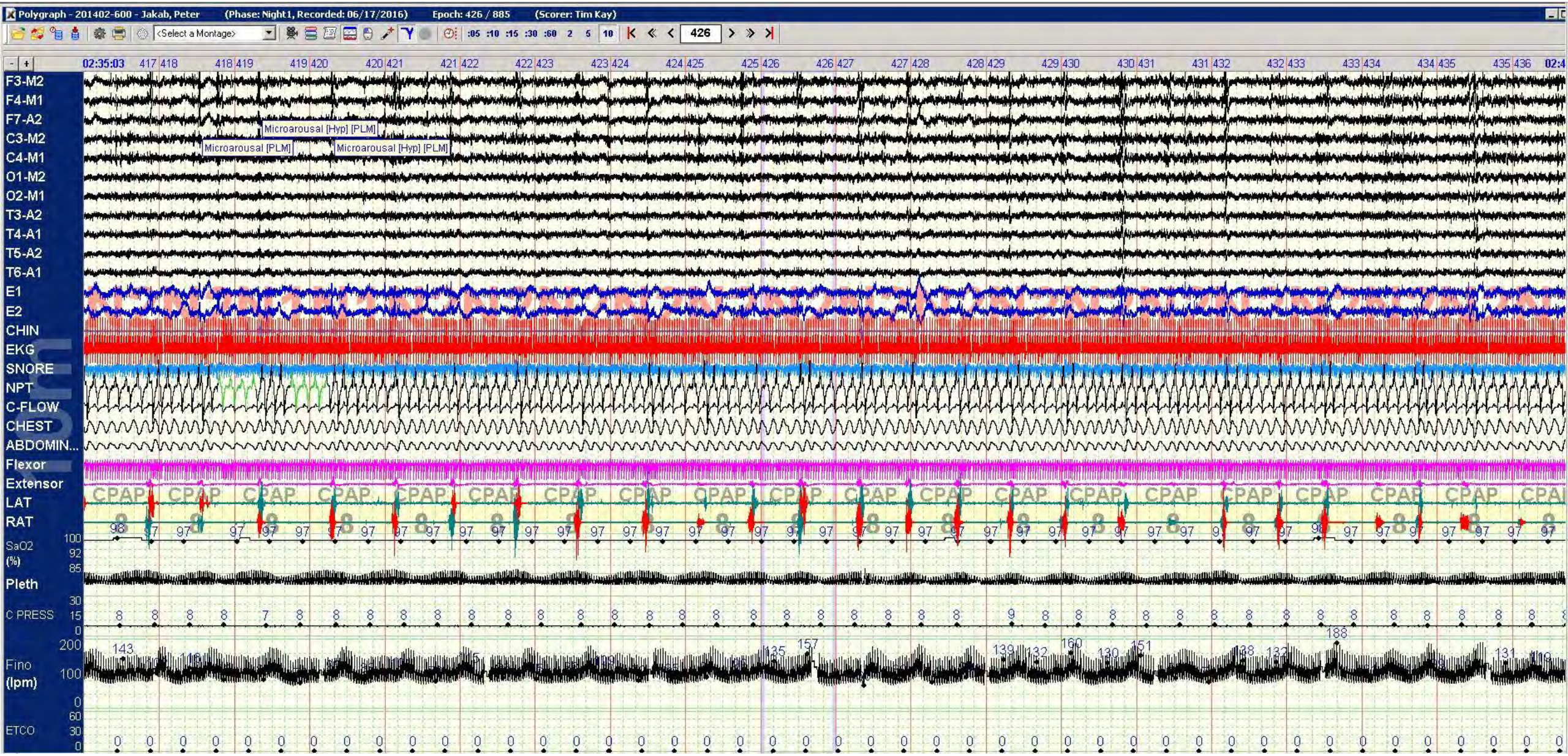
AWSTI


F3-M2
F4-M1
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
EKG
SNORE
C-FLOW
CHEST
ABDOMIN...
LAT
RAT
ETCO2
(mmHg)
WAV ETCO2
SaO2
(%)
Pleth
C PRESS
(cmH2O)
LEAK
Microarousal [Apn] [LM]
Microarousal [Apn]
Microarousal [Apn]
Microarousal [Apn]
SUPINE
CPAP

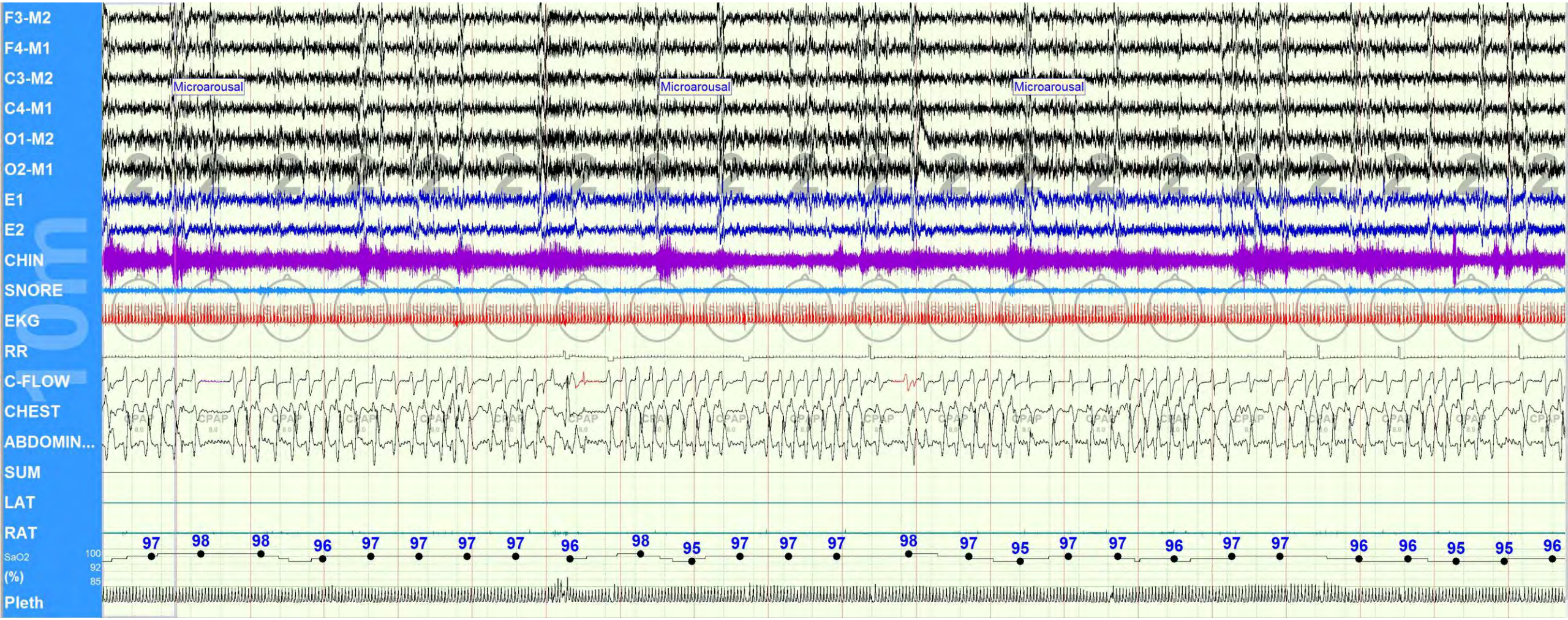
Alternating PLMS +variable network coupling



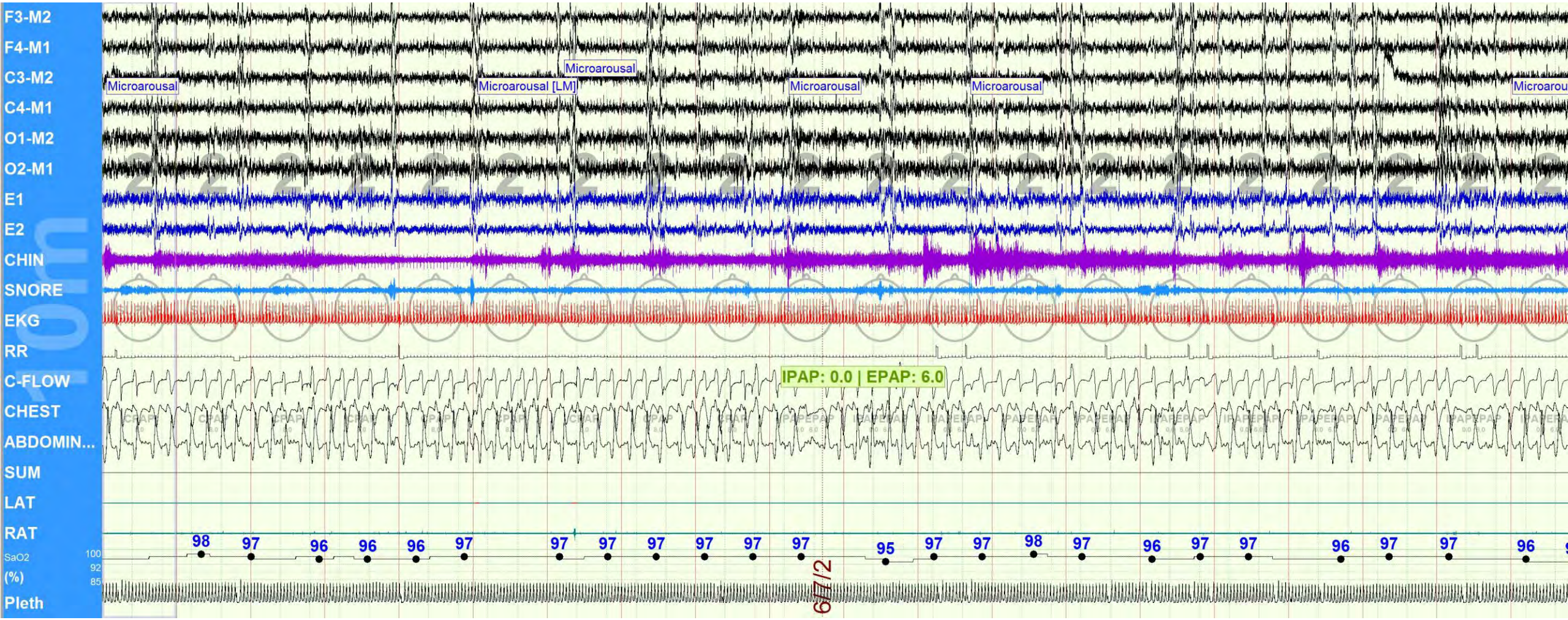

F3-M2
F4-M1
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
SNORE
NPT
THERM
CHEST
ABDOMIN...
LAT
RAT
EKG
SaO2 (%)
Pleth
Microarousal
Microarousal [PLM]
Microarousal [PLM]
Microarousal [PLM]
Microarousal [PLM]
N2 N2 N2 N2 N2 N3 N3 N3 N3
100
92
85
96 96 97 97 97 96 96 96 96 96 96 97 97 96 96 96 96 96 96 96 96 97 97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


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

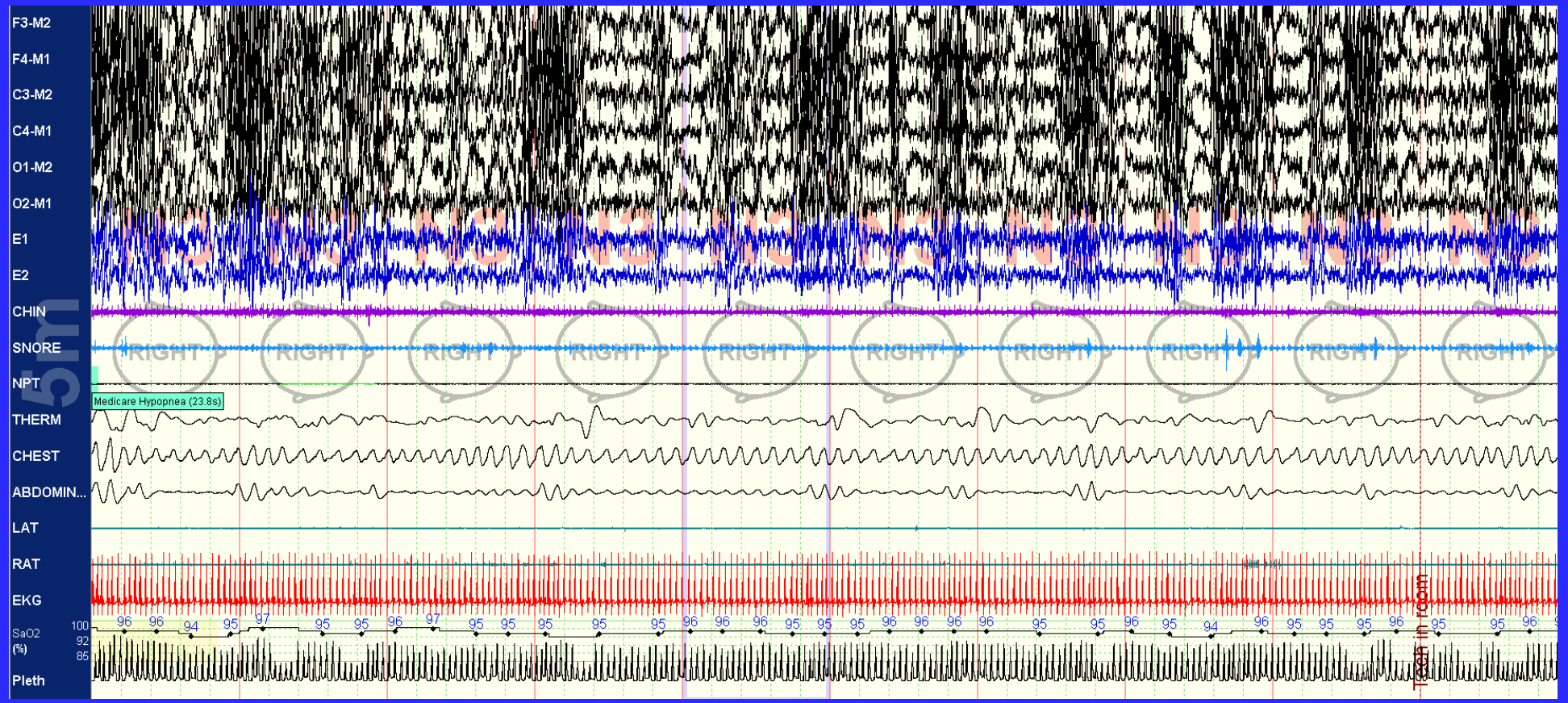
Cortico-motor network

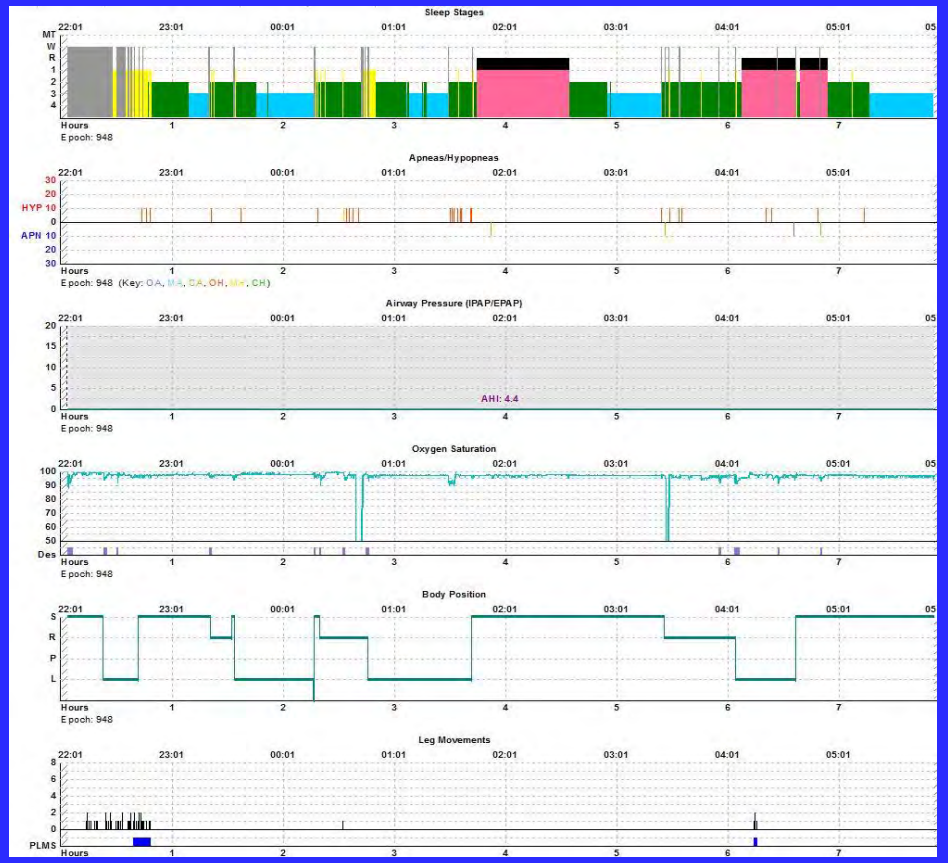


Cortico-motor network

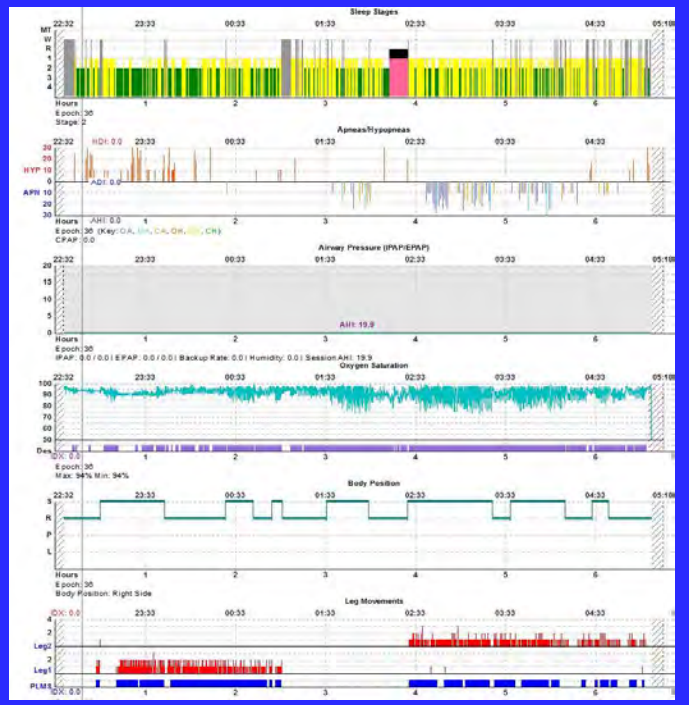


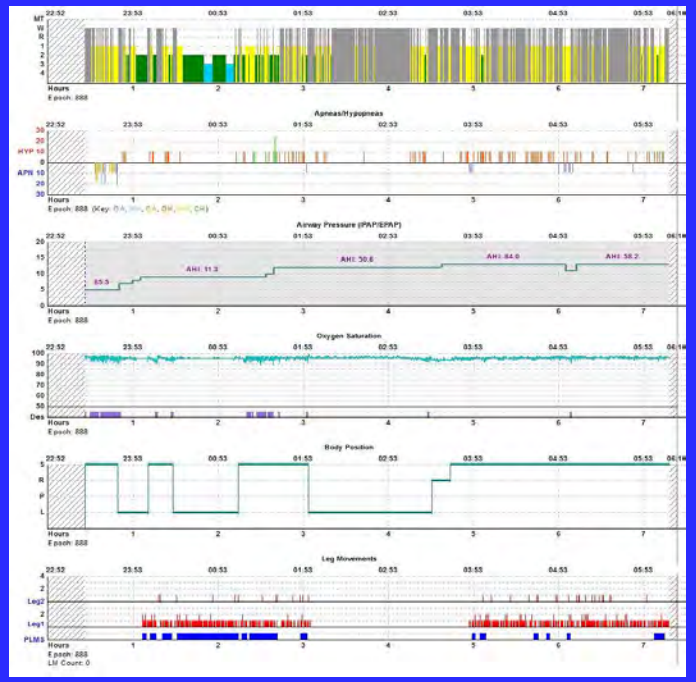
N3 CAP (5-minute)





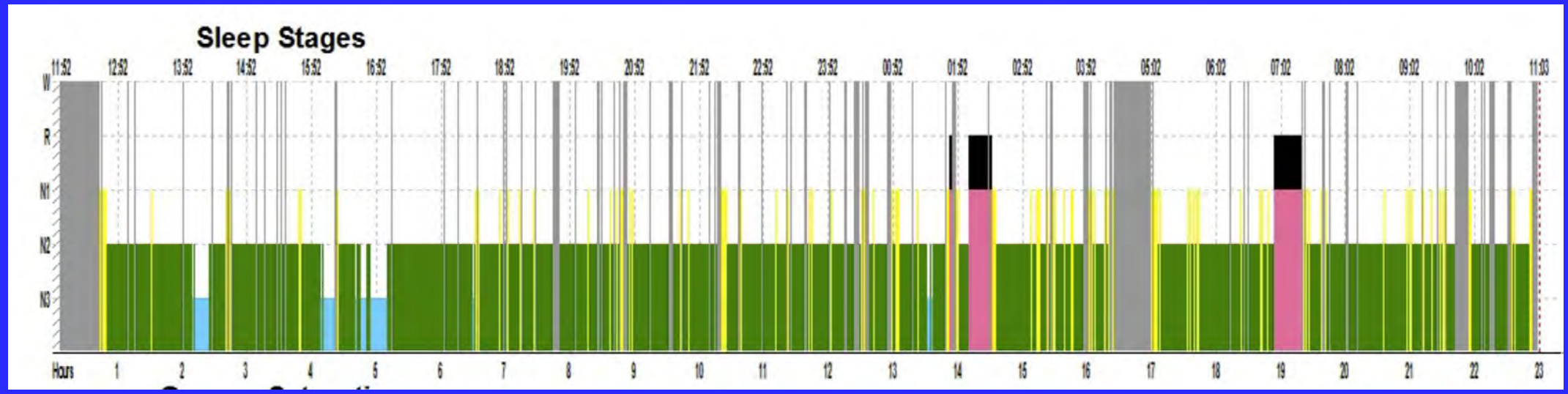
Network success





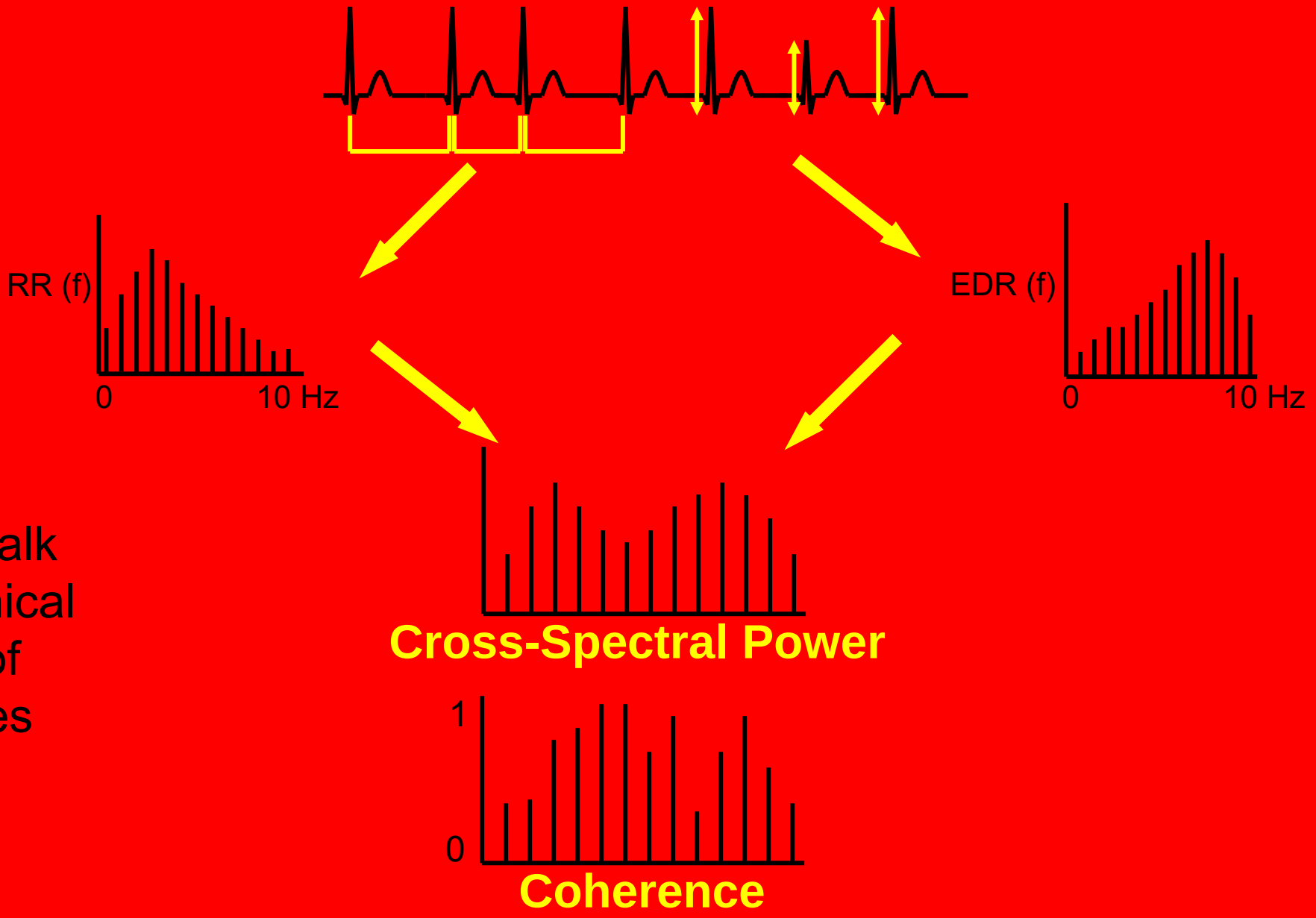
Network failure!

Idiopathic hypersomnia: network-off failure



A speculative word on idiopathic hypersomnia

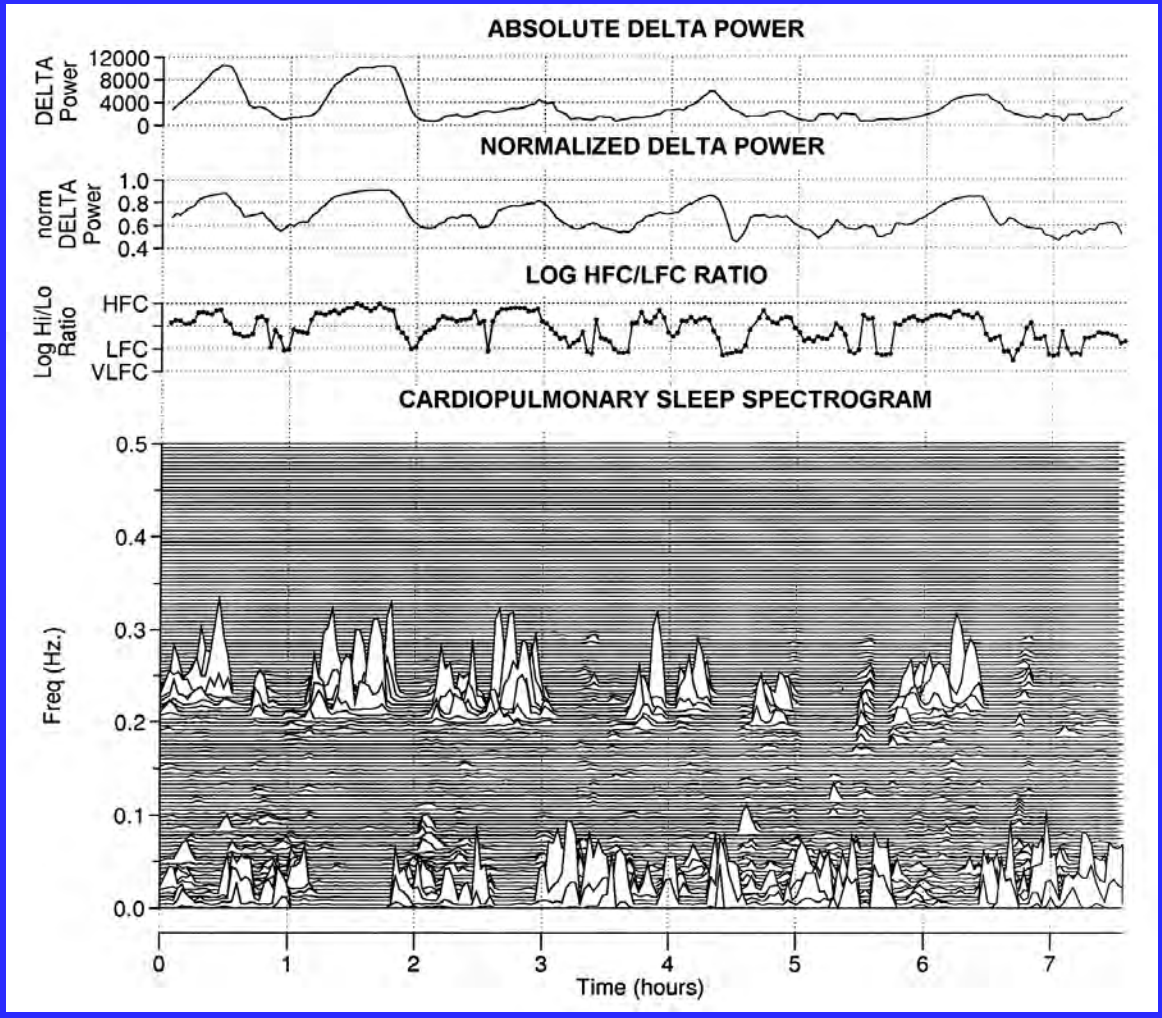
- Relevant to all hypersomnias with substantial sleep inertia
- A network transition disorder
- Pathological persistence of sleep network = long sleep
- Pathological inability to switch off for wake network = sleep inertia
- Mixed sleep-wake network persistence = fog
- Stimulants do not work well due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



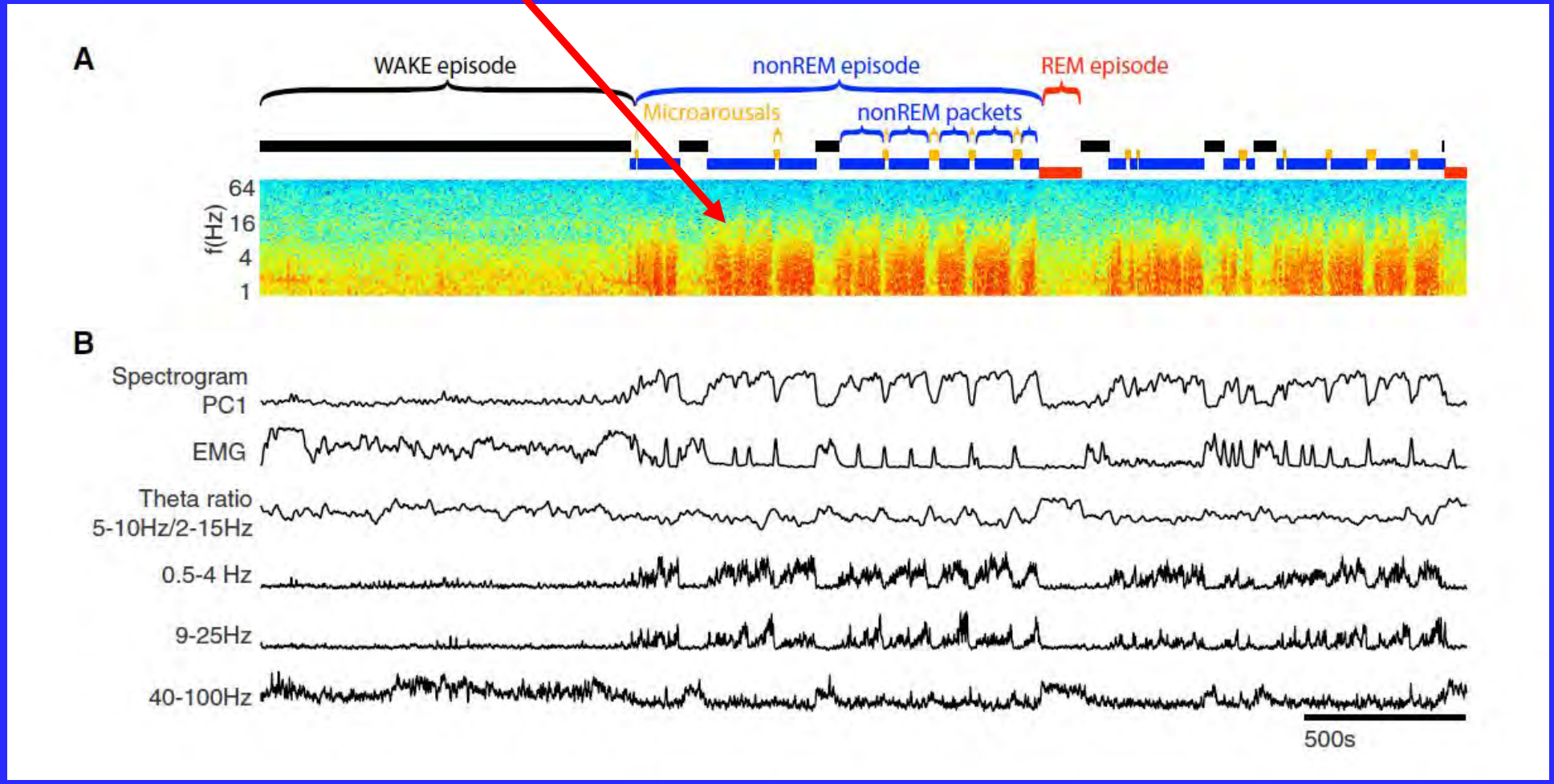
Now we talk about clinical tracking of instabilities

Cardiopulmonary Coupling =
$[\text{Cross-Spectral Power}]^2 \times [\text{Coherence}]$

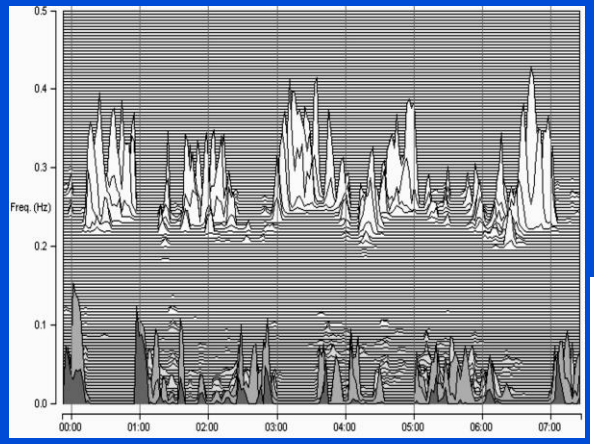
Slow wave power and ECG-spectrogram

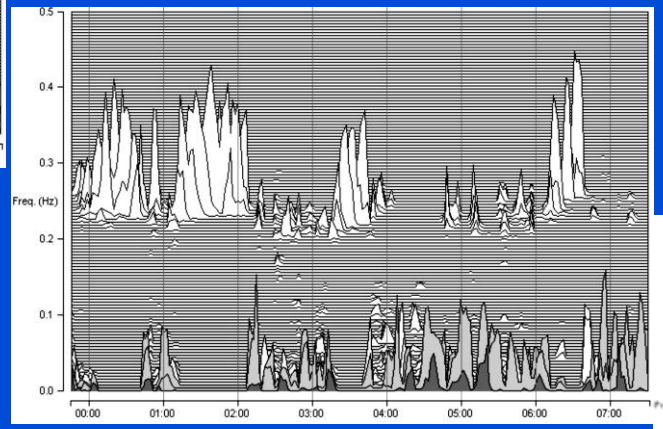


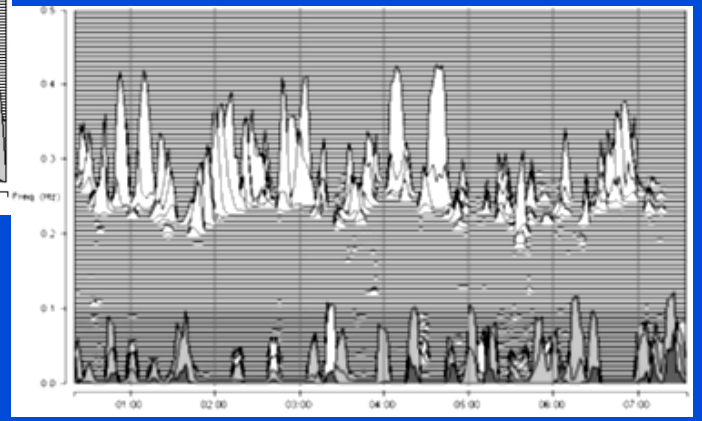
Direct recording from the cortex of rodents show that NREM occurs in “packets”

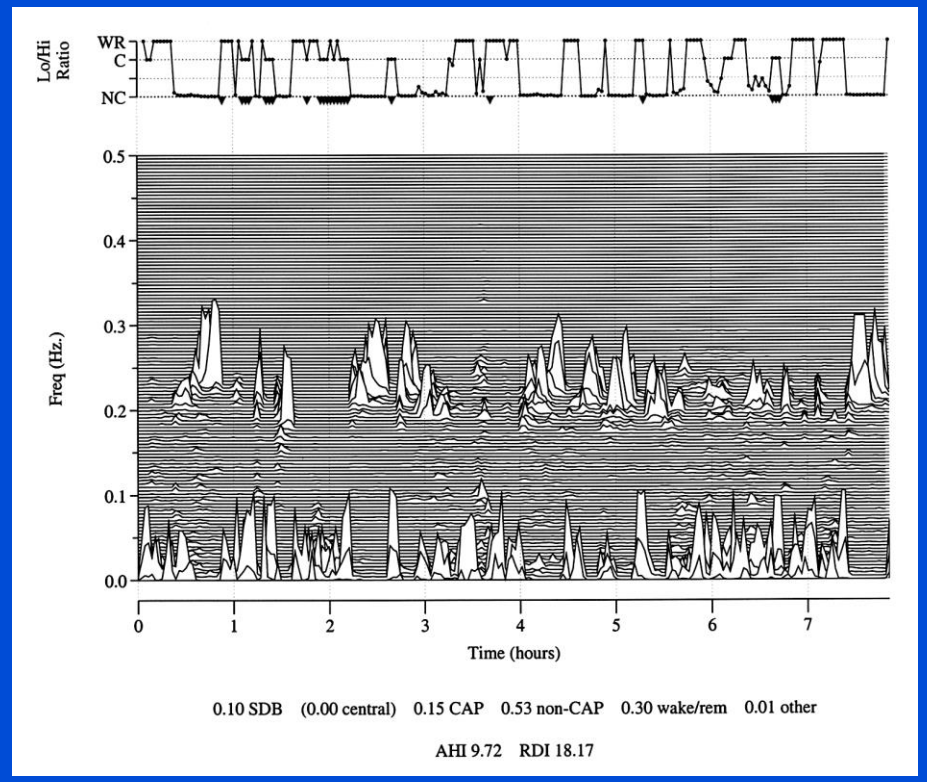


Night-to-night stability



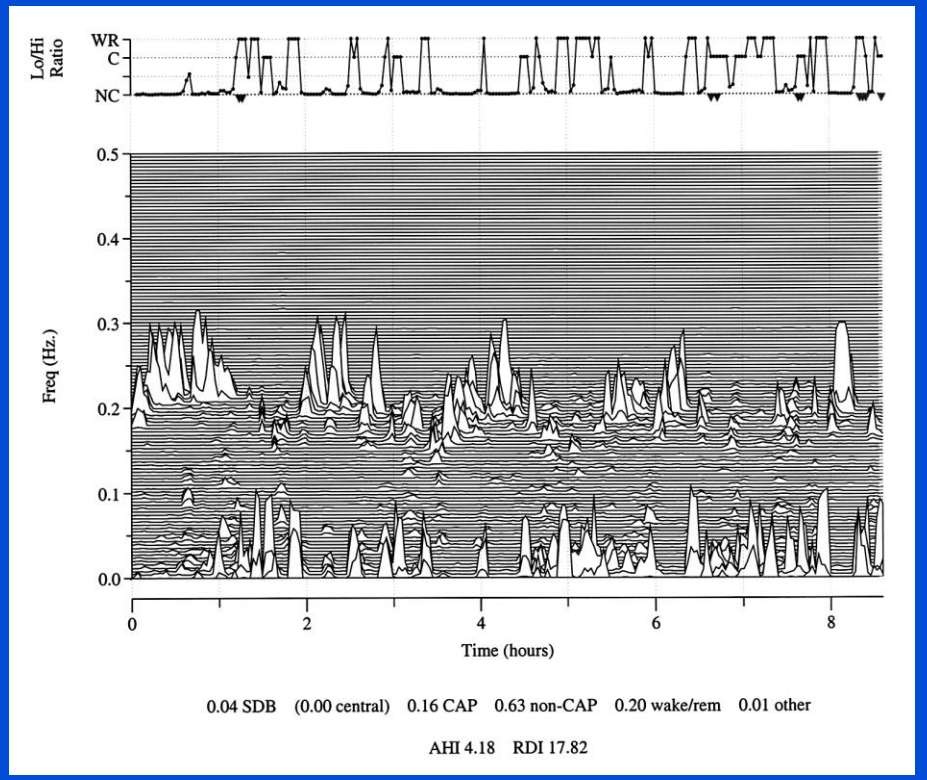




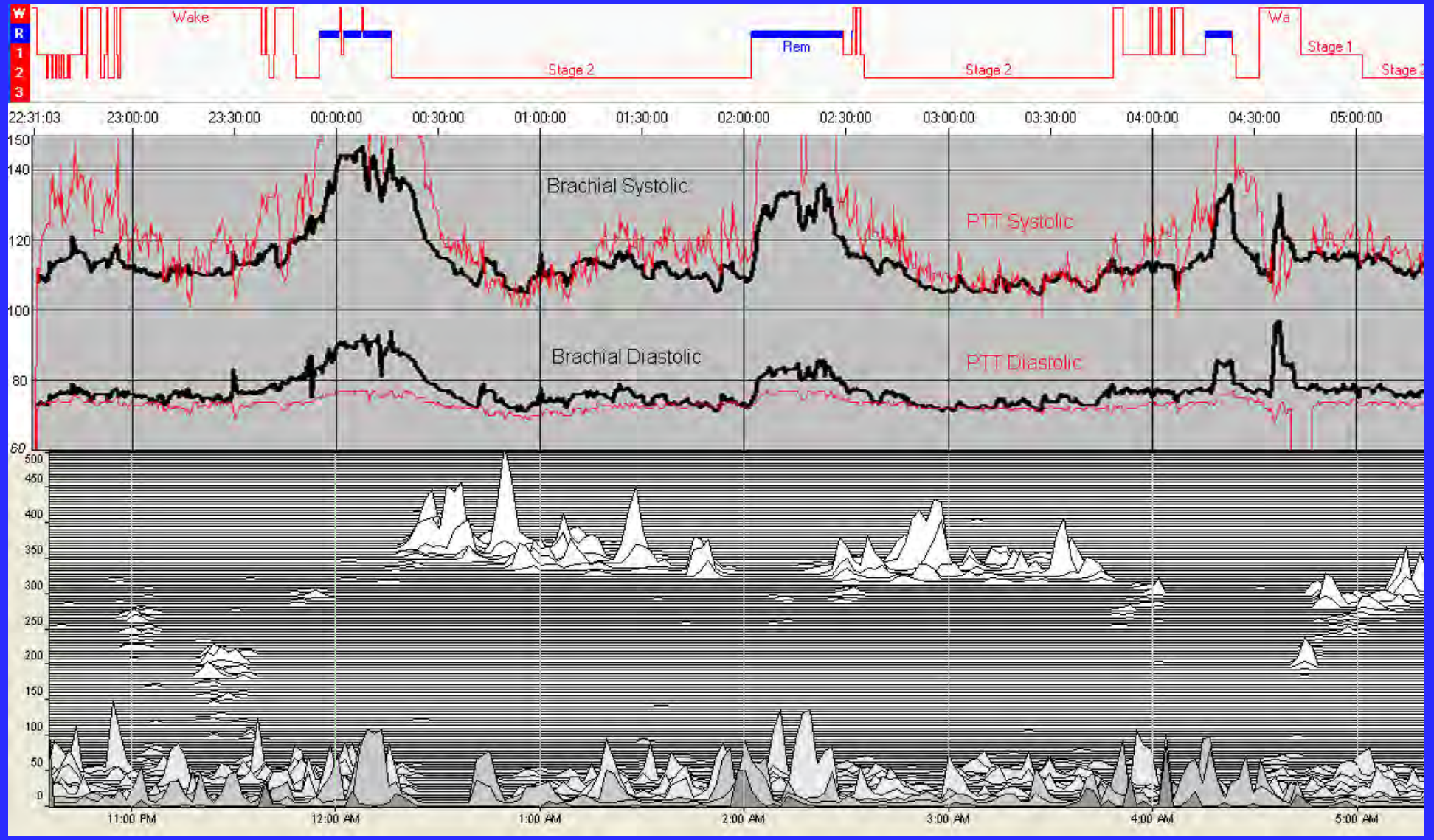


Rested - human

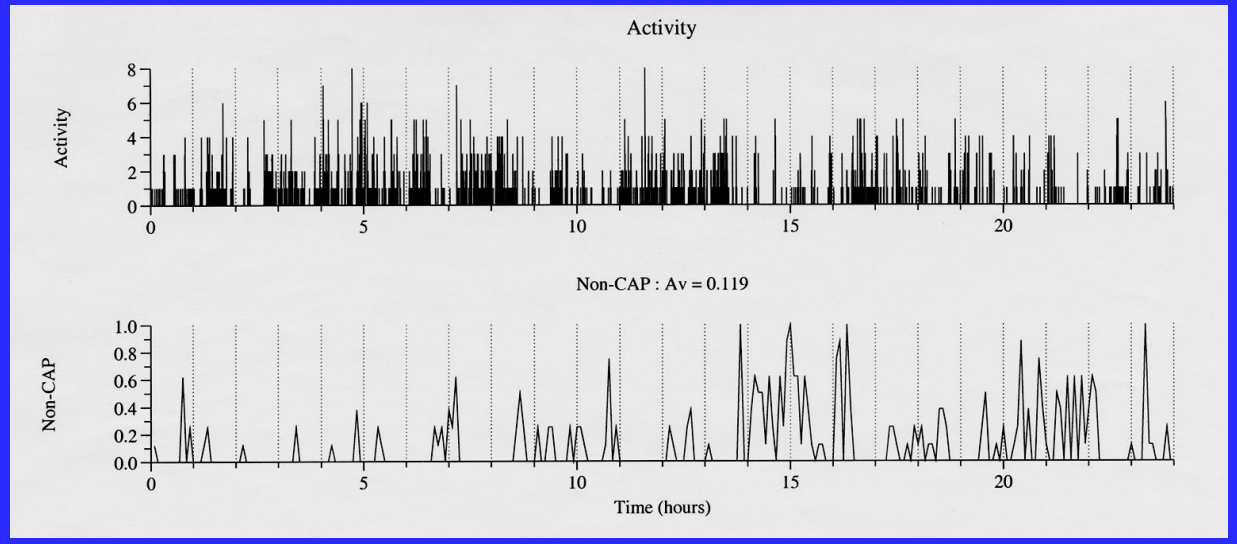
Sleep deprivation recovery – increased HFC all across the night



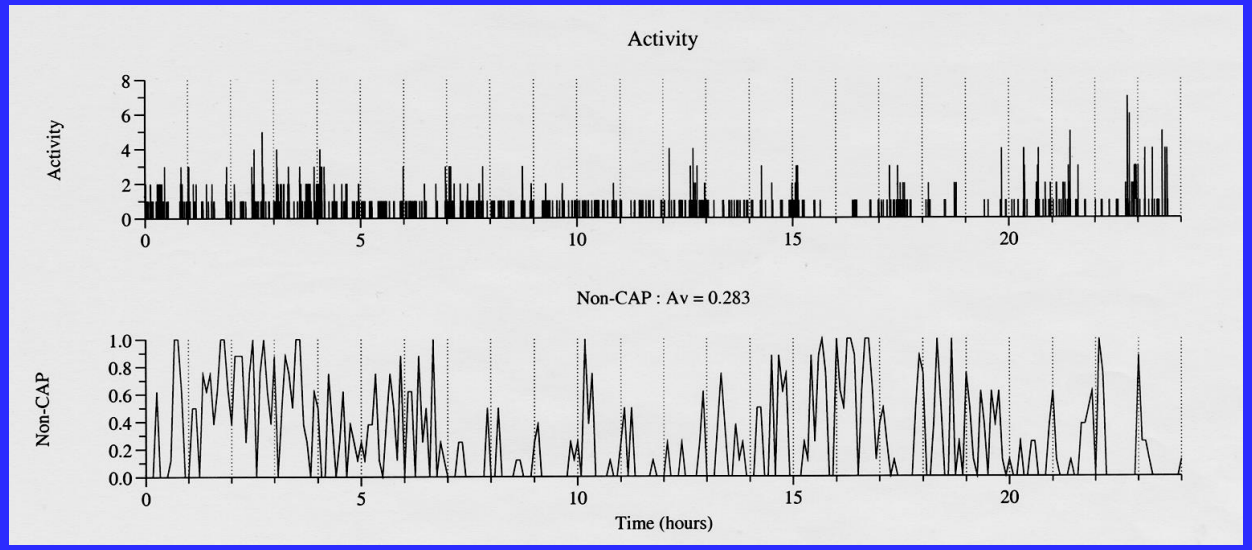
Blood pressure “dips” only during the periods of high frequency coupling



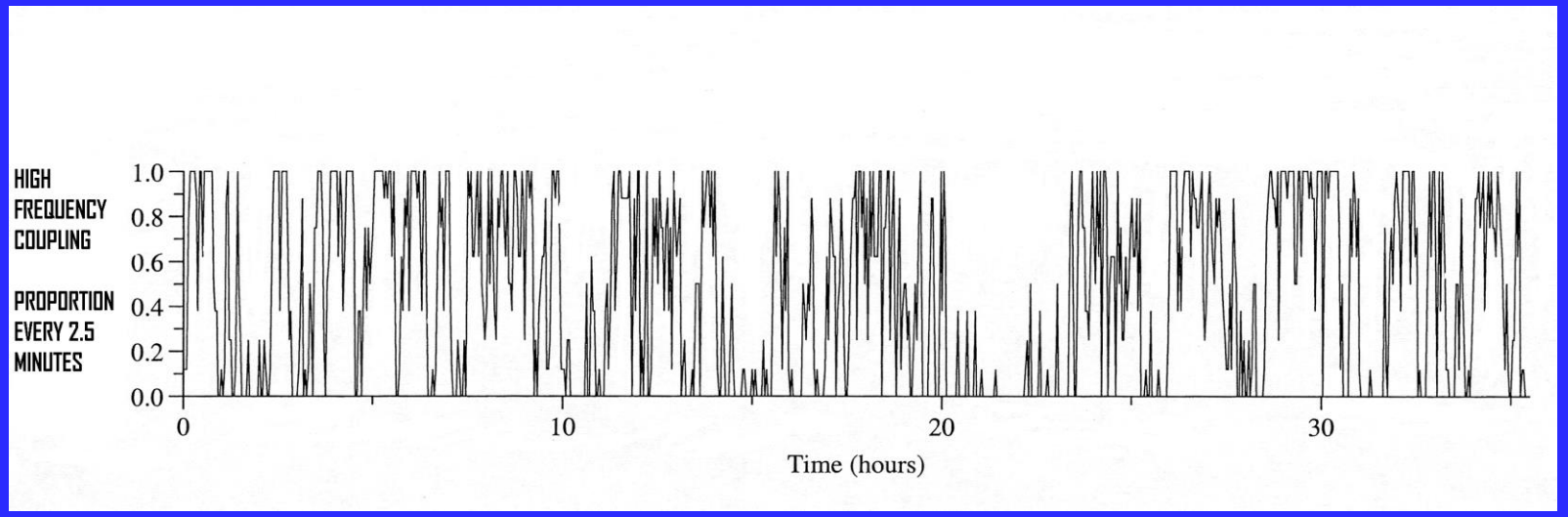
Benzodiazepines decrease slow wave but increases integrated stability (rat data)

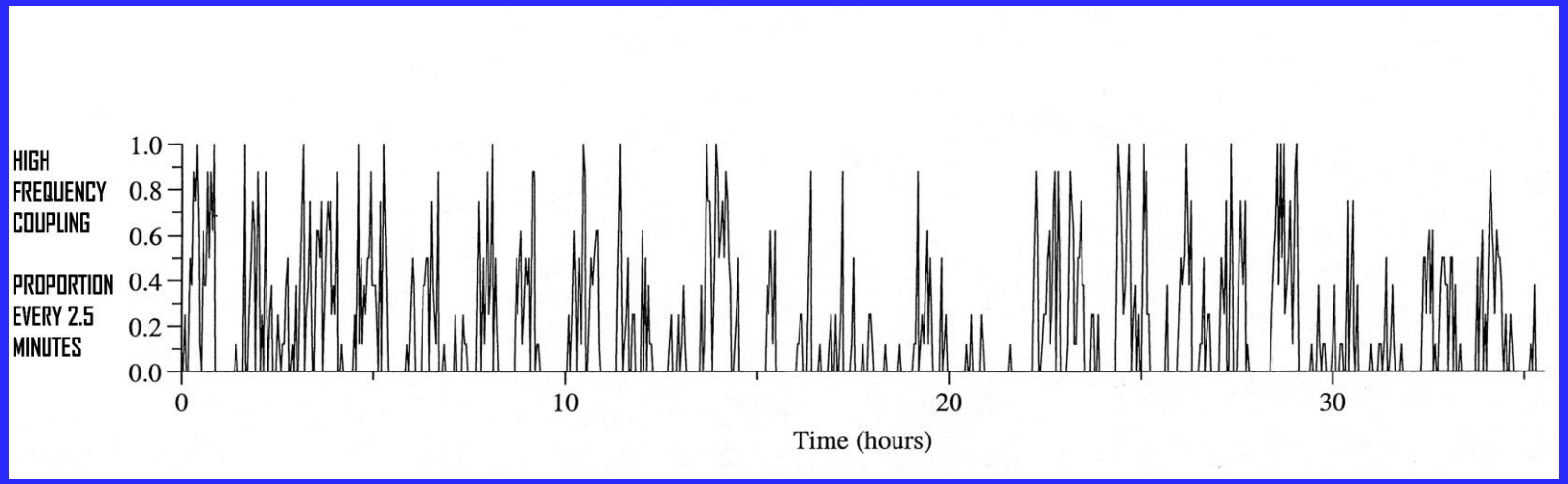


Lorazepam 0.9 mg/Kg/day

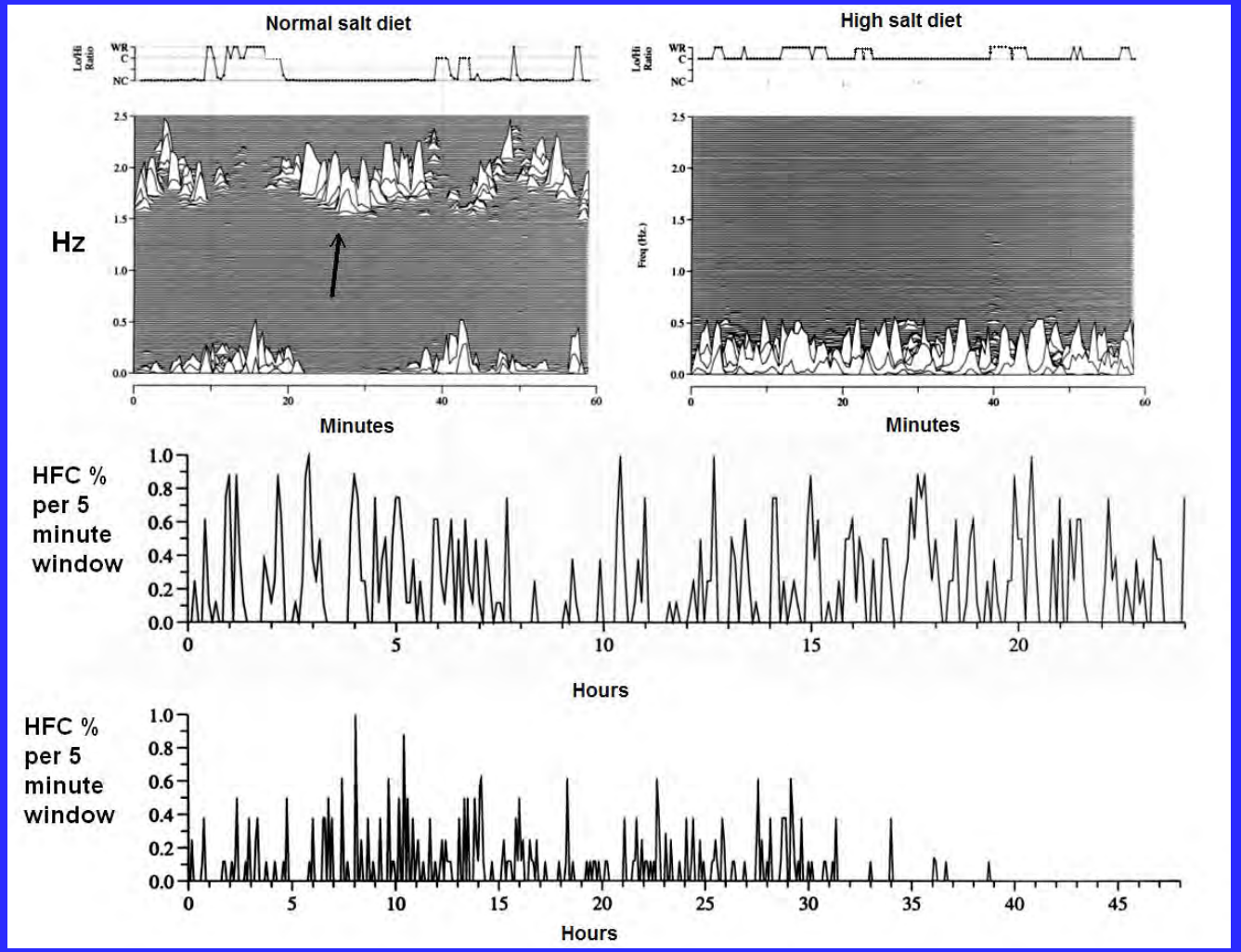


Sleep network fragmentation in Alzheimer's disease (transgenic mouse)

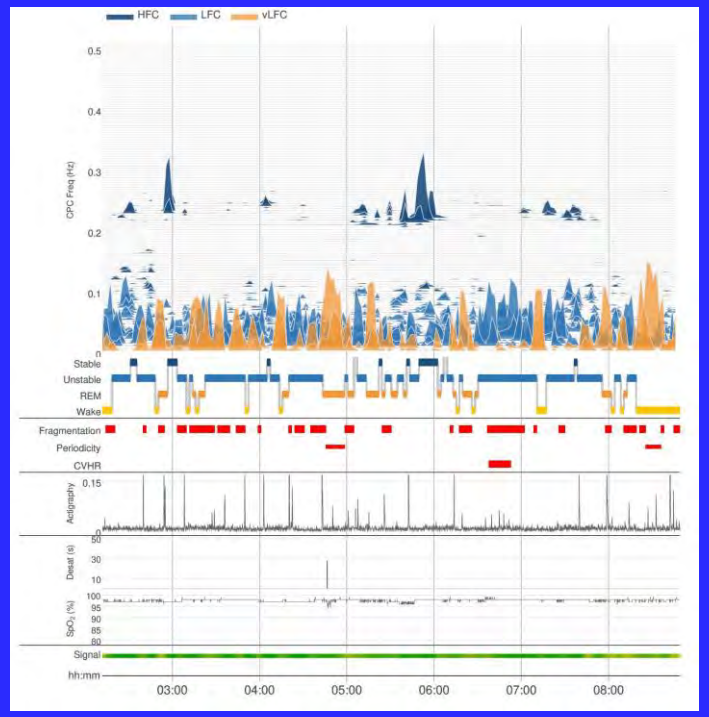


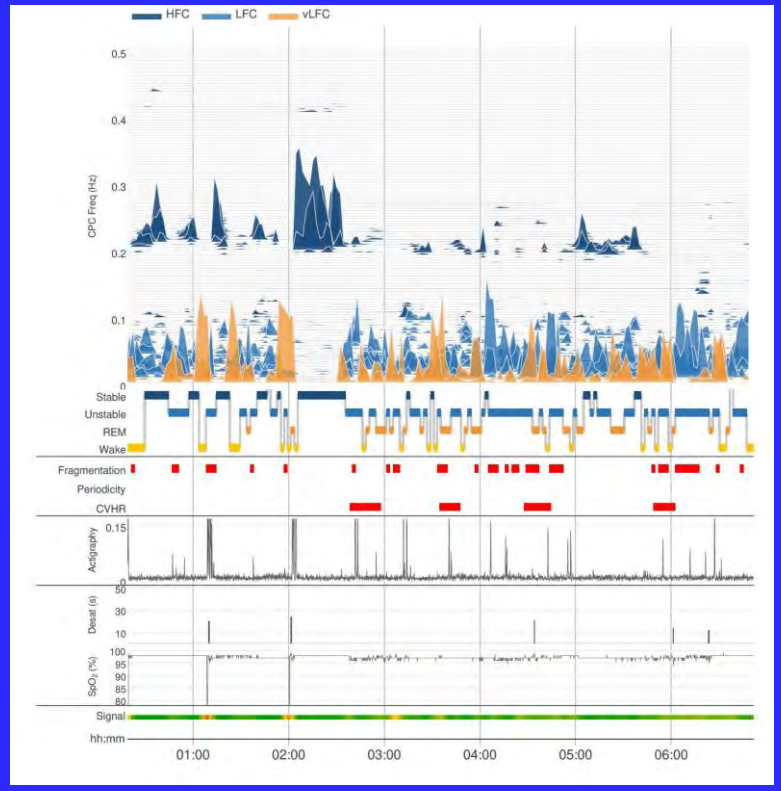


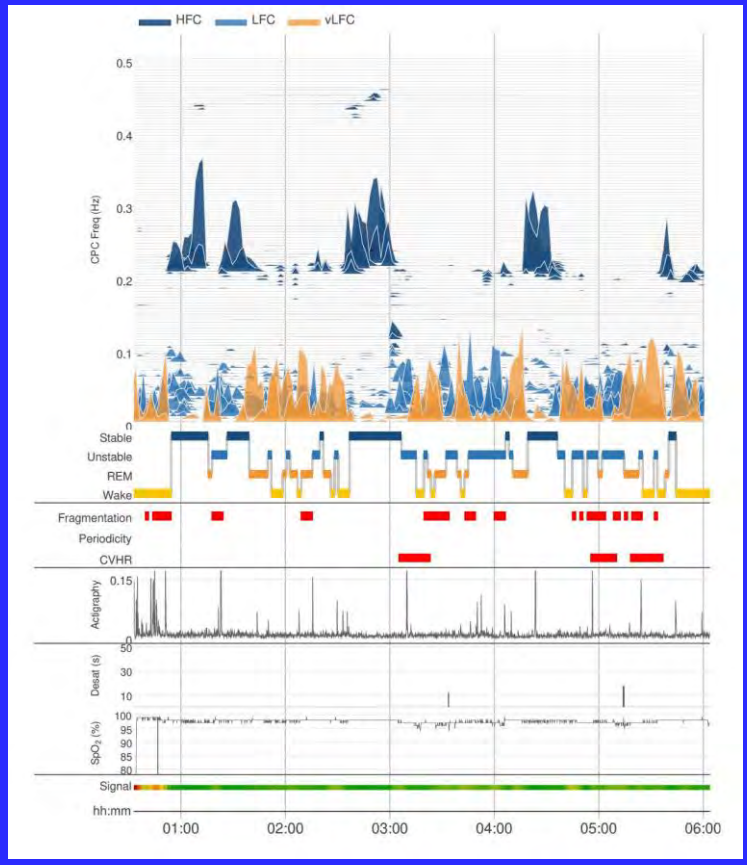
Sleep network fragmentation in heart failure



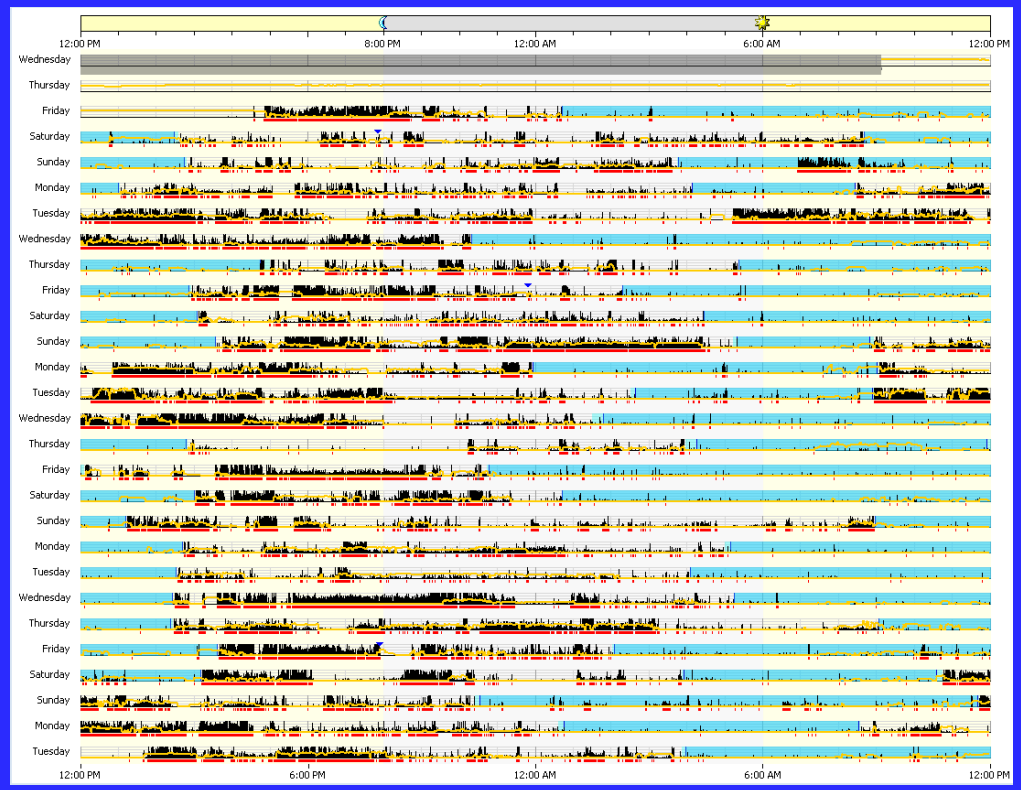
Sleep quality instability

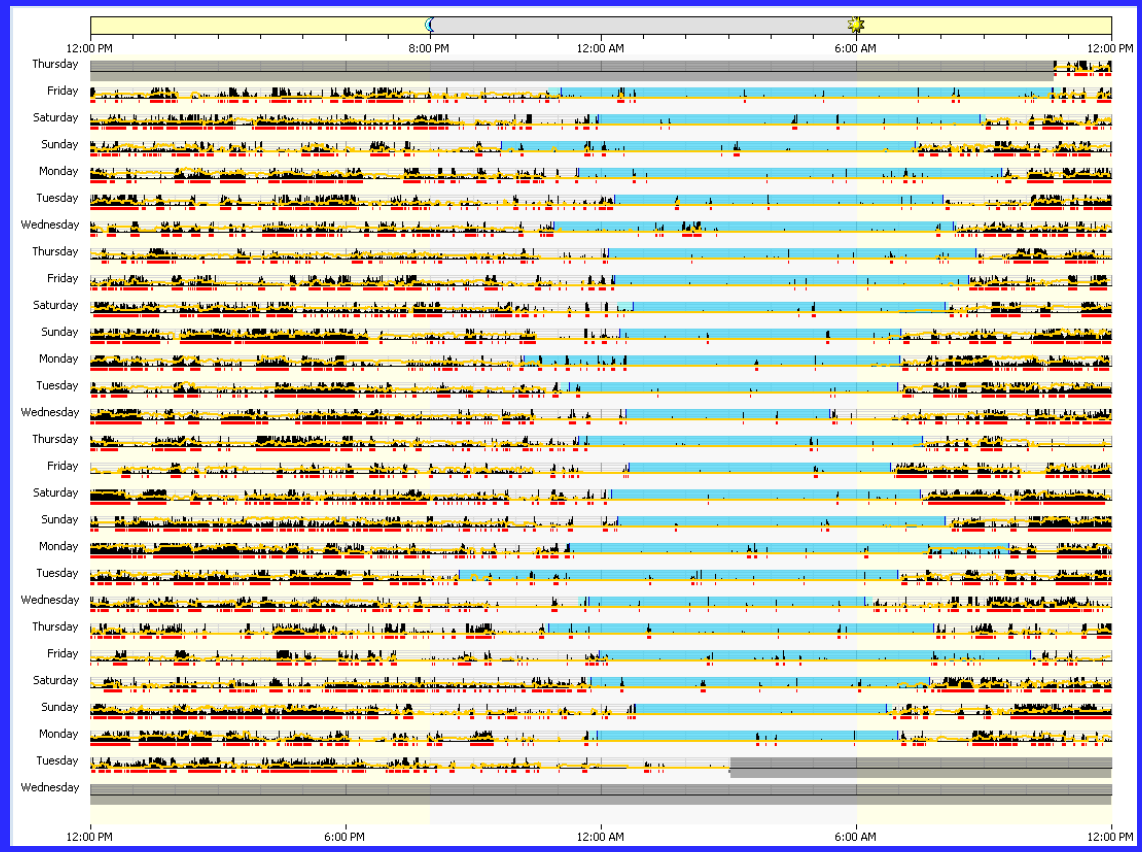






Sleep timing instability – pre/post lithium





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