Sleep as a Network State (Part I)

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Conflict of Interest Disclosures for Speakers

☐ 1. I do not have any relationships with any entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, **OR**

☒ 2. I have the following relationships with entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients.

Type of Potential Conflict	Details of Potential Conflict
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Consultant	Jazz Pharmaceuticals, Guidepoint Global, GLG Councils
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Financial support	
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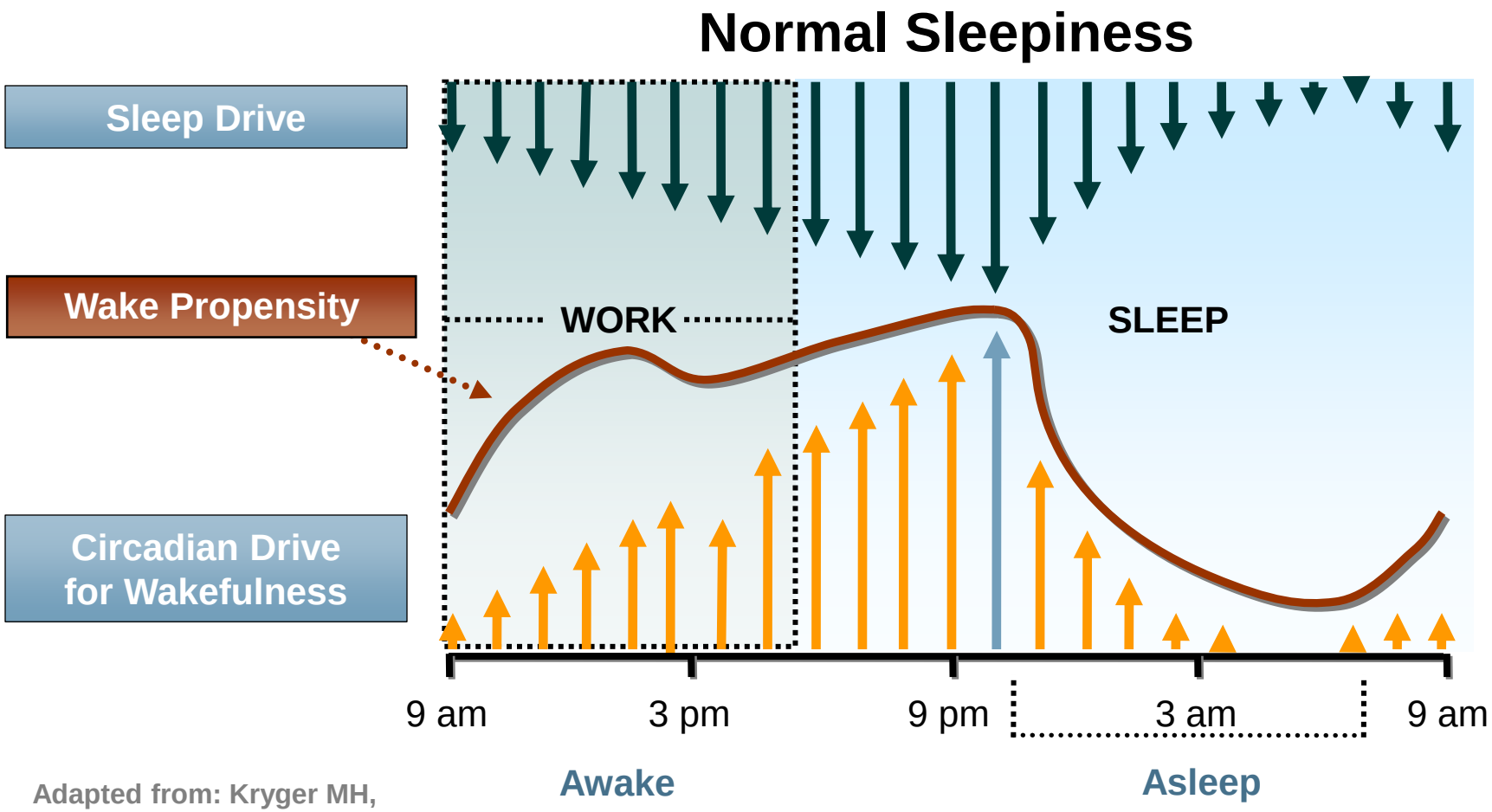
☒ 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

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

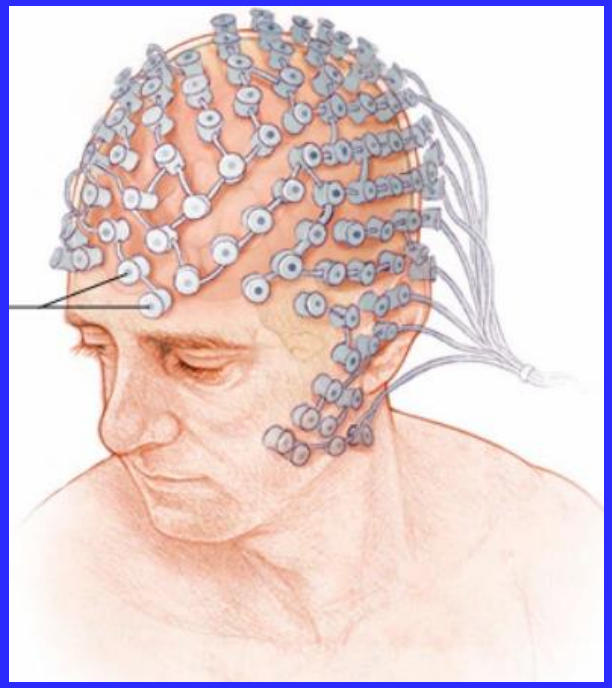
Physiologic Determinants of Sleepiness



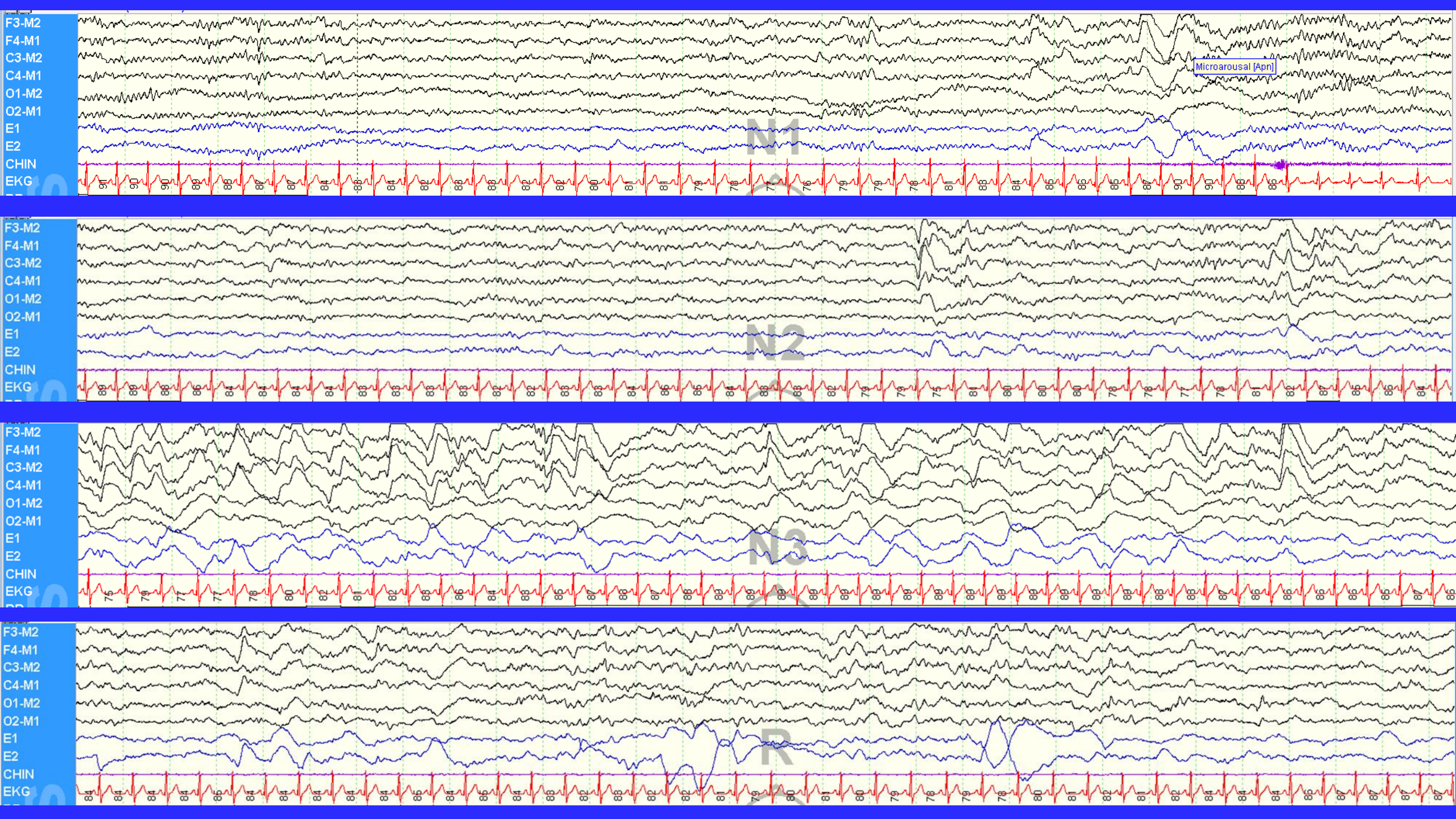
Adapted from: Kryger MH, et al. Principles and Practices of Sleep Medicine. 2000.

Measurement of sleep

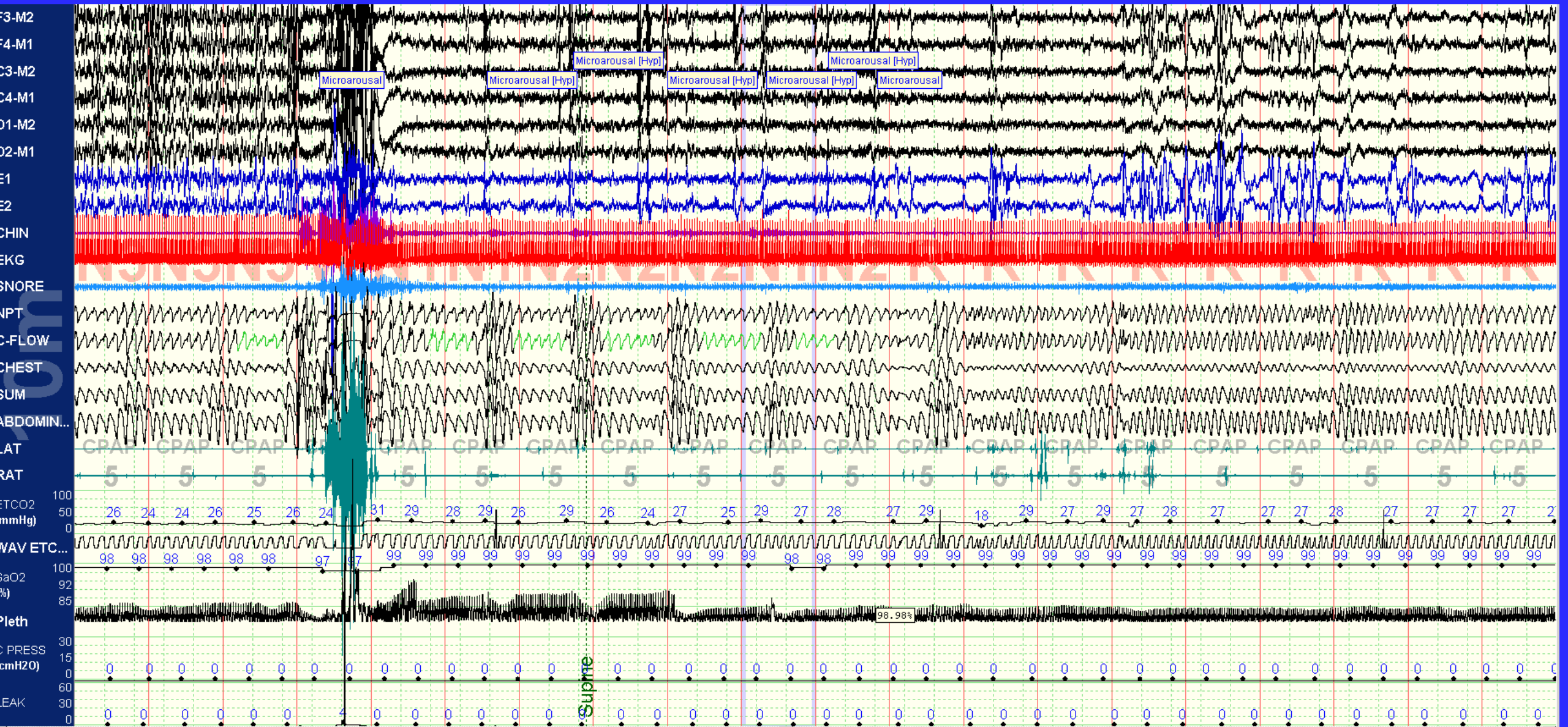
- Classic EEG based
- Dense array EEG
- Respiratory
- Autonomic
- Movement
- Blood biomarkers
- Gene expression / transcriptome



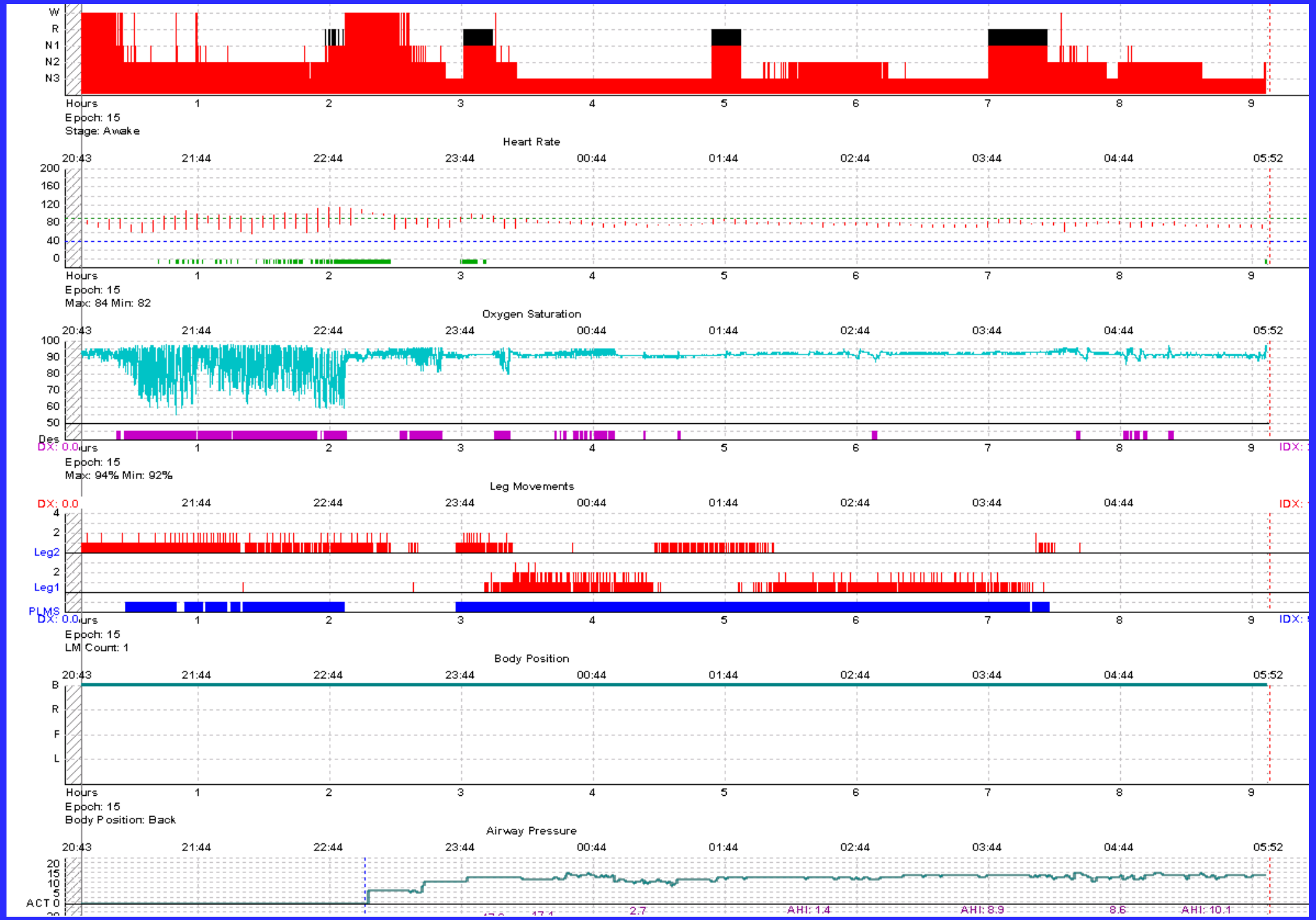

fineart
america


F3-M2
F4-M1
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
EKG
Microarousal [Apn]
N1
N2
N3
R

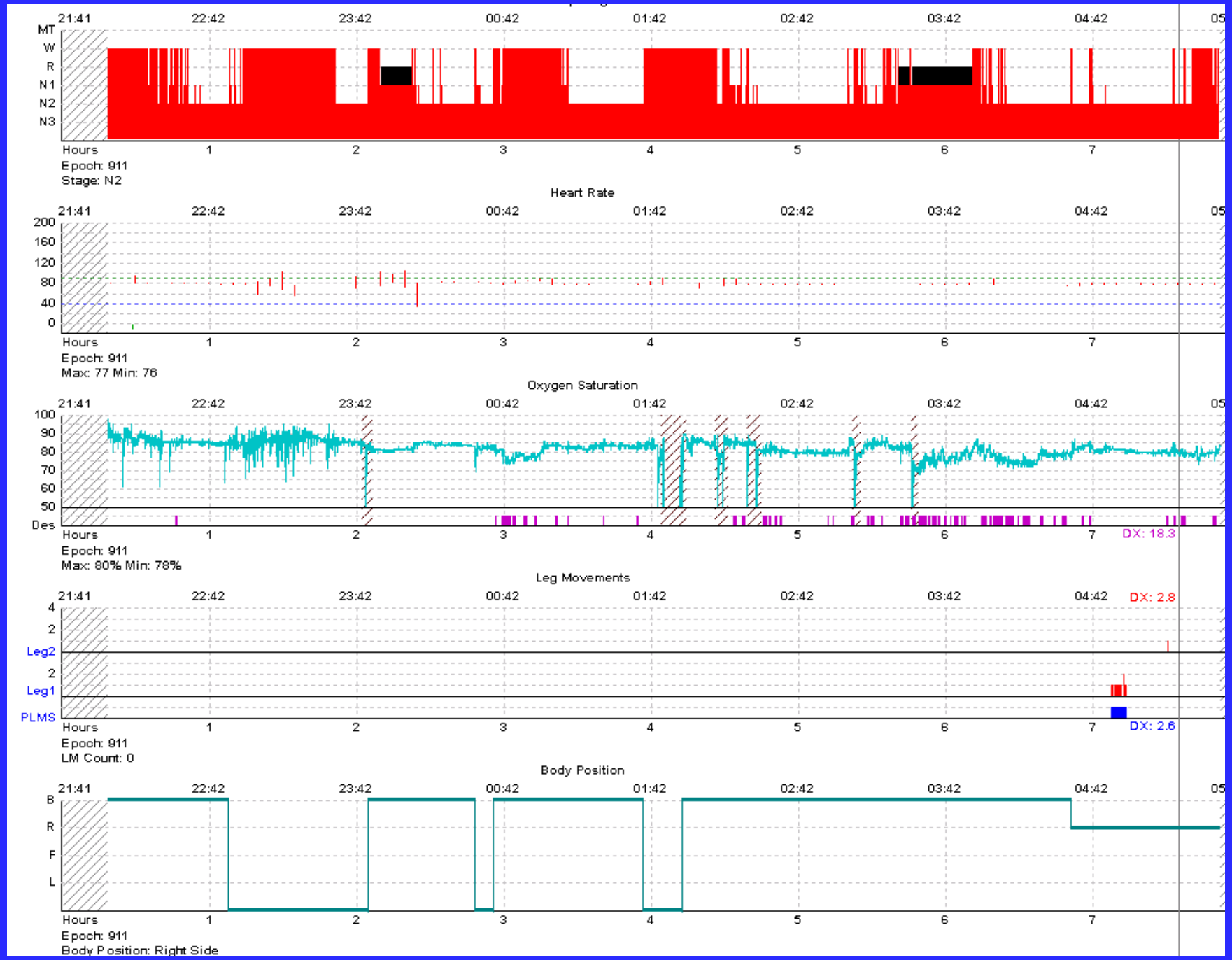
Classic Polysomnogram



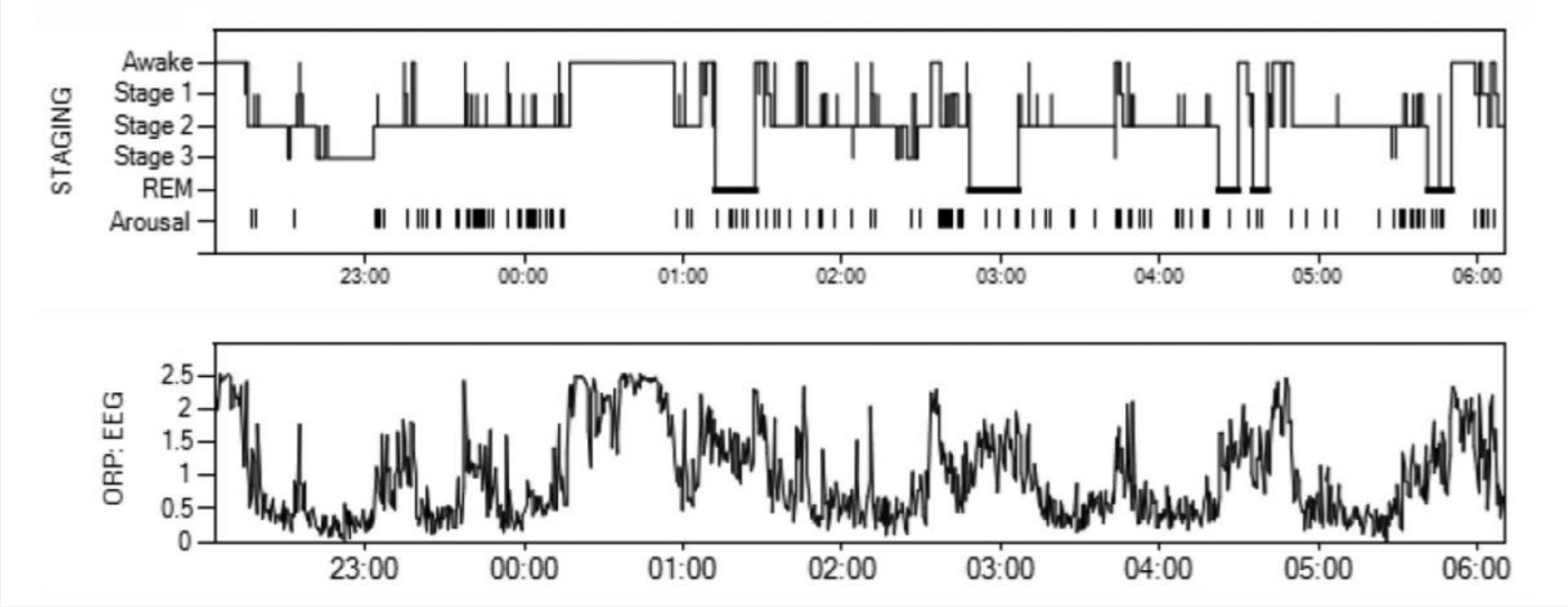
Classic Split Night



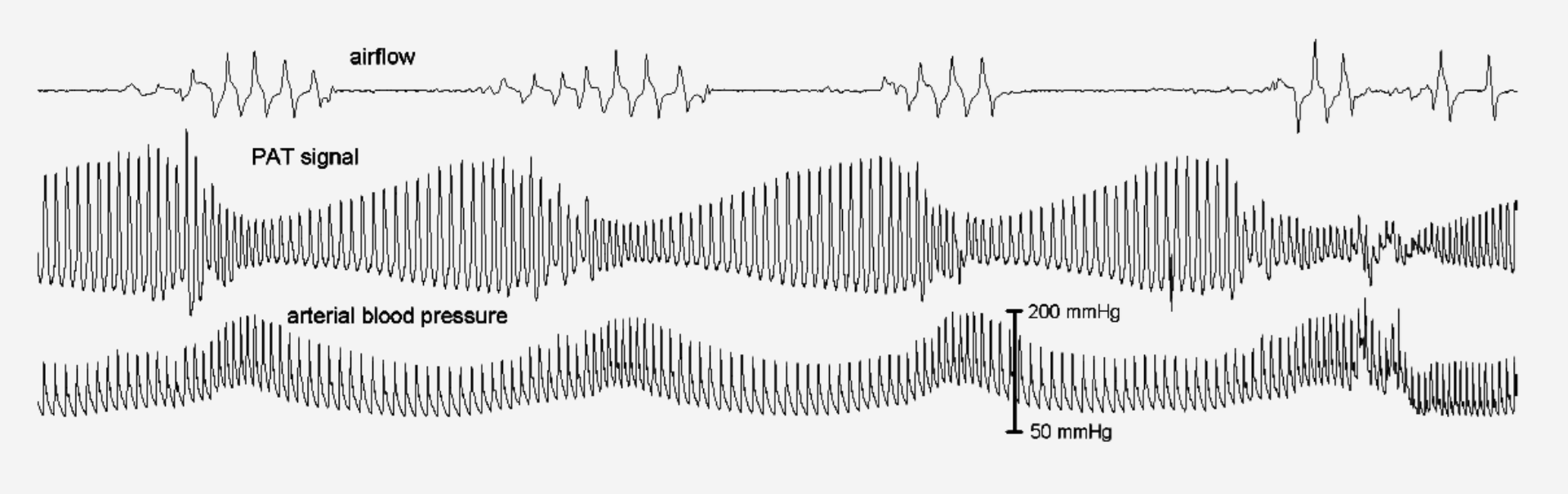
Macro-frag


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

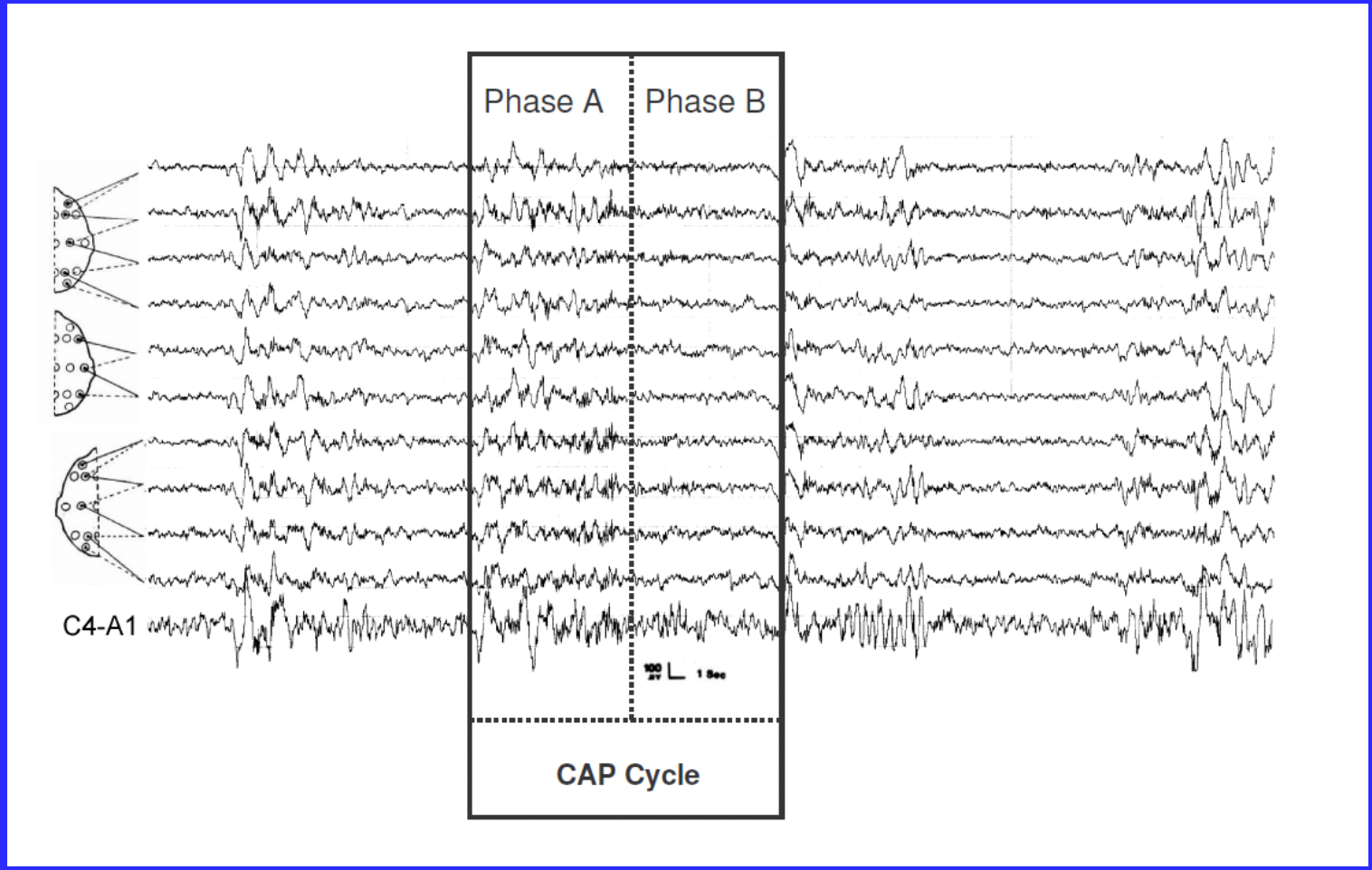
Standard signal, novel analysis (ORP)



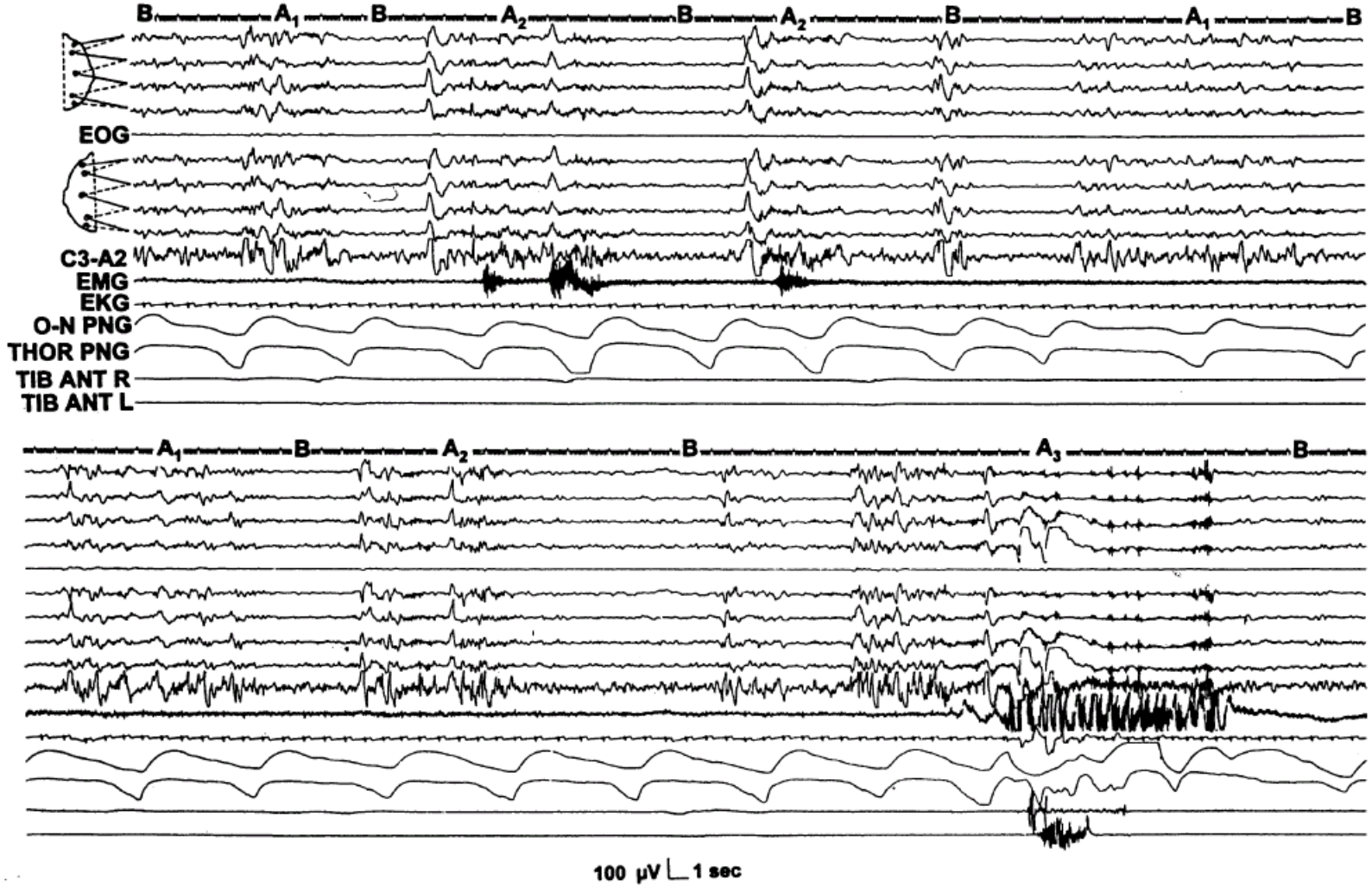
Multiple coupled sleep subsystems – respiration, autonomic drive, blood pressure



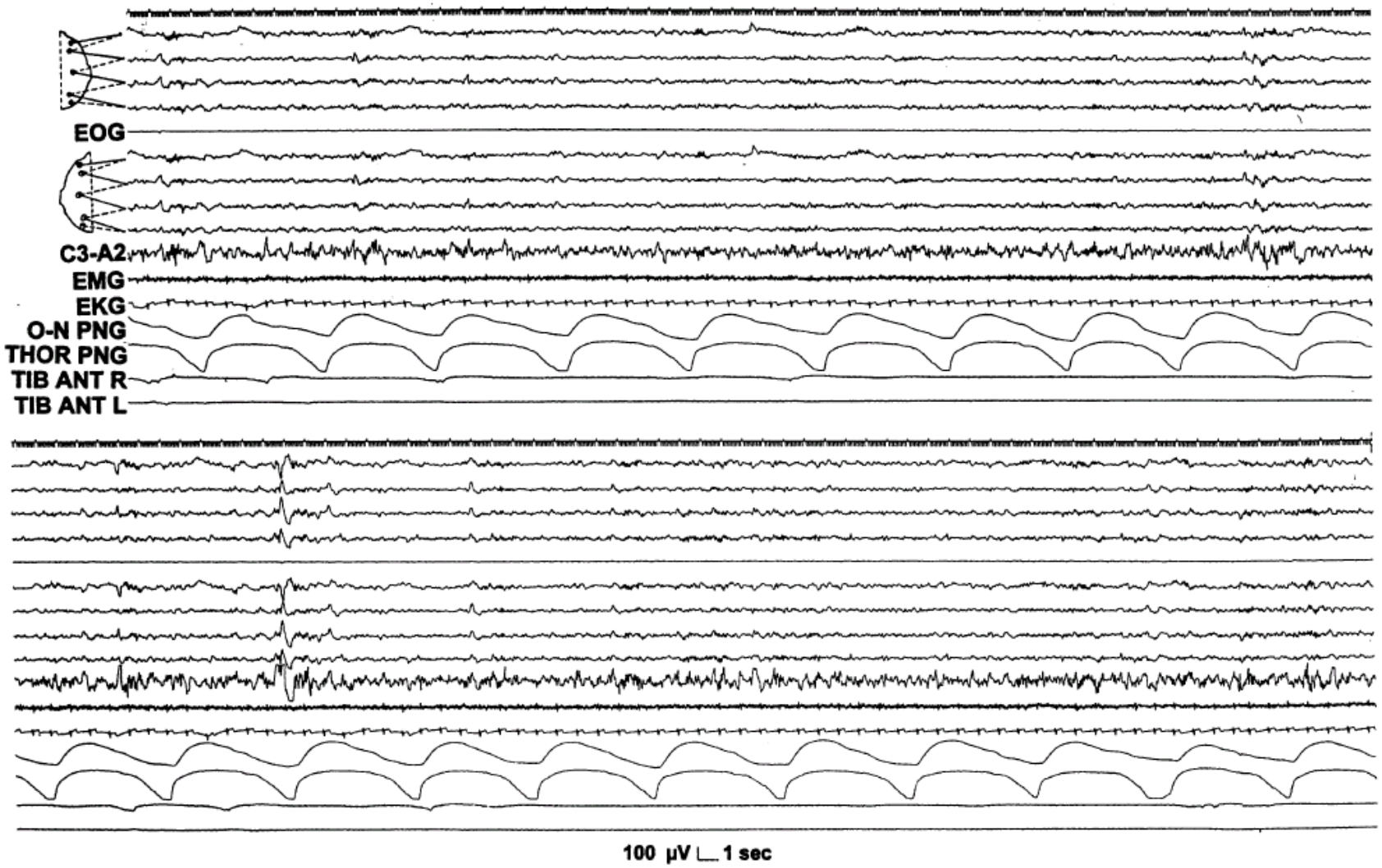
Cyclic Alternating Pattern (CAP)



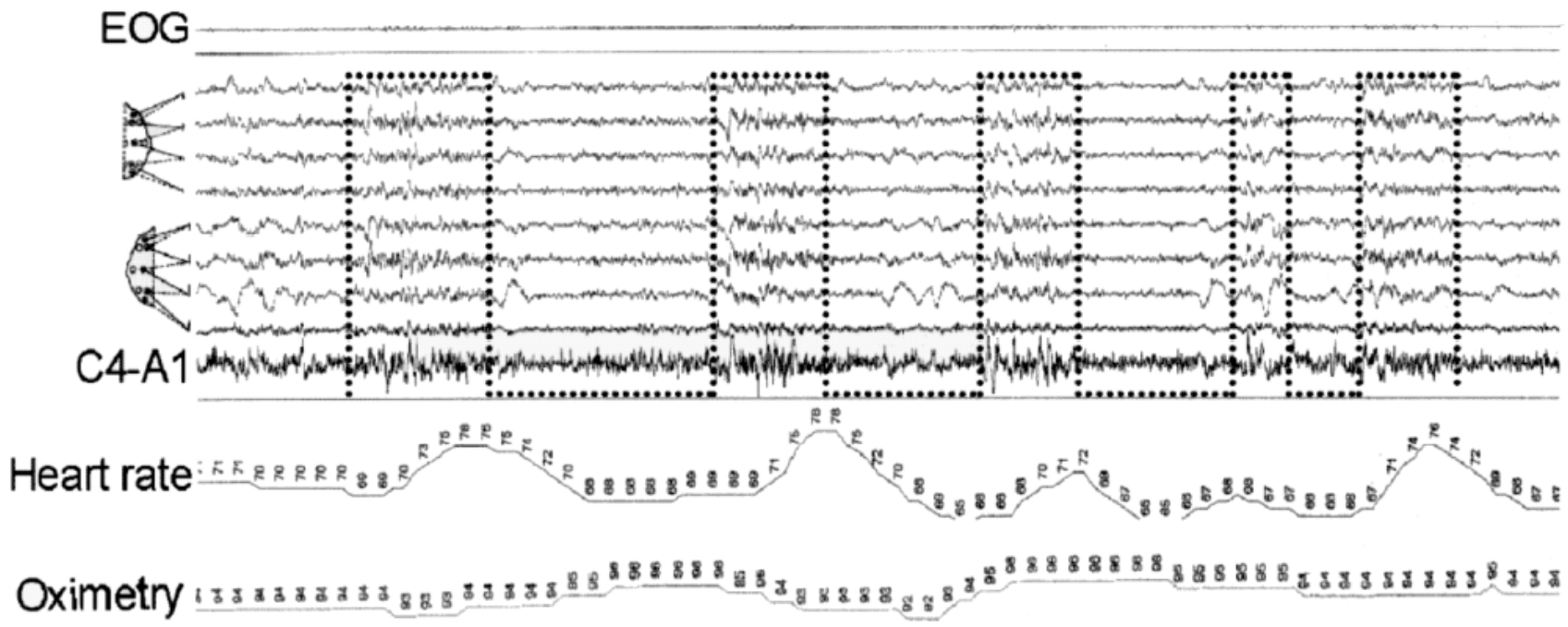
A period of CAP which can go on for tens of minutes, markedly amplified in disease

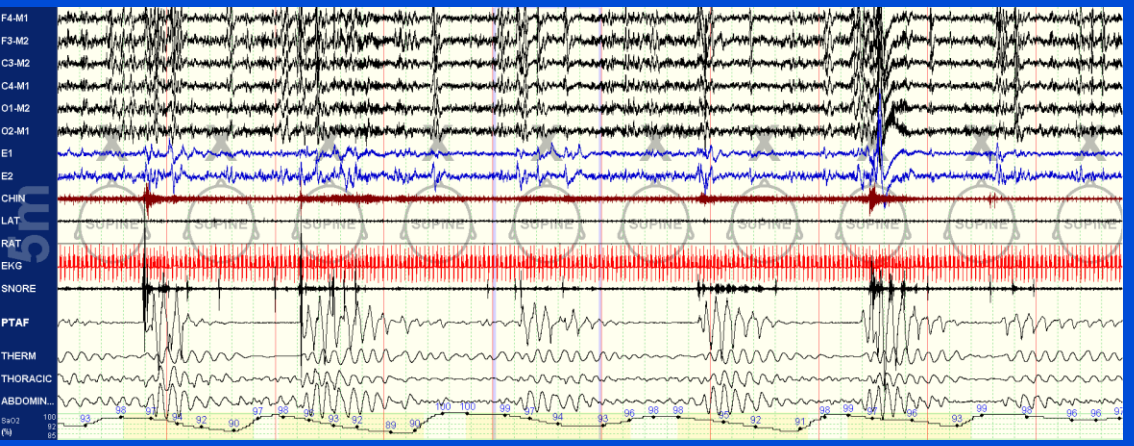


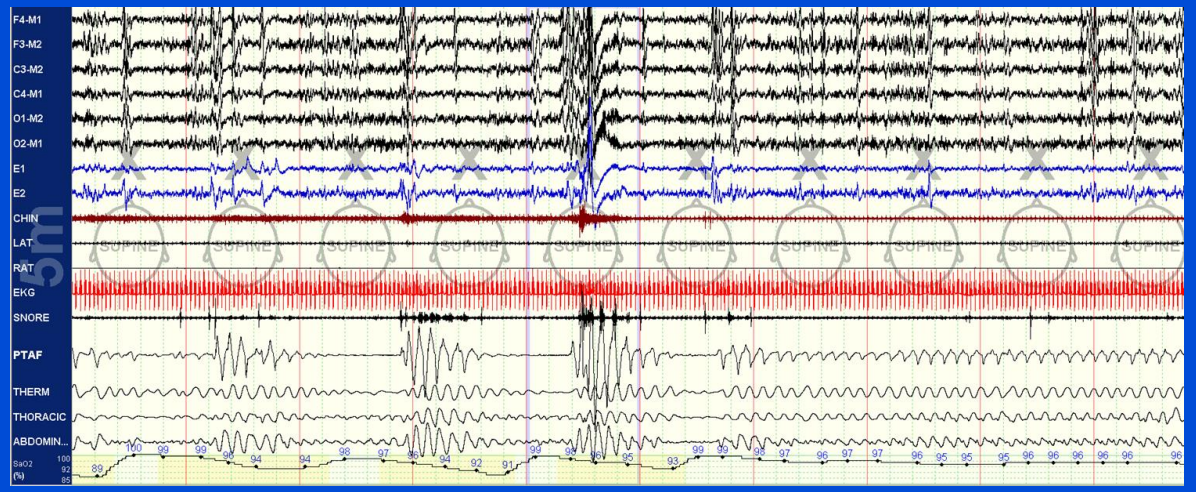
A period of EEG quiescence, which can go on for tens of minutes

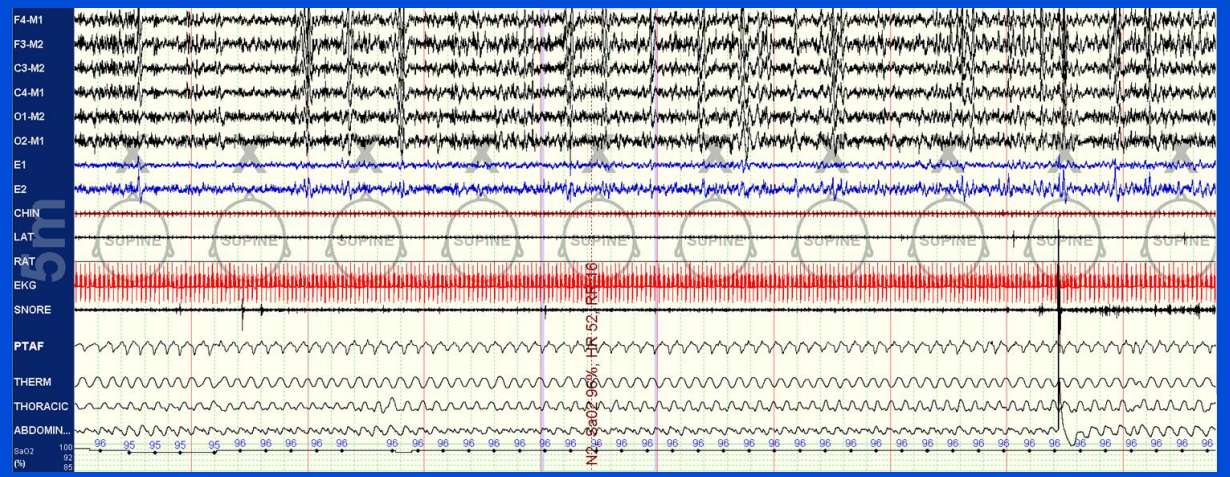


EEG and ECG and linked




F4-M1
F3-M2
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
LAT
RAT
EKG
SNORE
PTAF
THERM
THORACIC
ABDOMIN...
SaO2 (%)
SUPINE
5m


F4-M1
F3-M2
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
LAT
RAT
EKG
SNORE
PTAF
THERM
THORACIC
ABDOMIN...
SaO2 (%)
SUPINE
5m


F4-M1
F3-M2
C3-M2
C4-M1
O1-M2
O2-M1
E1
E2
CHIN
LAT
RAT
EKG
SNORE
PTAF
THERM
THORACIC
ABDOMIN...
SaO2 (%)
SUPINE
5m
N2 SaO2 96%, HR 52, RR 16

Sleep is a unique network state

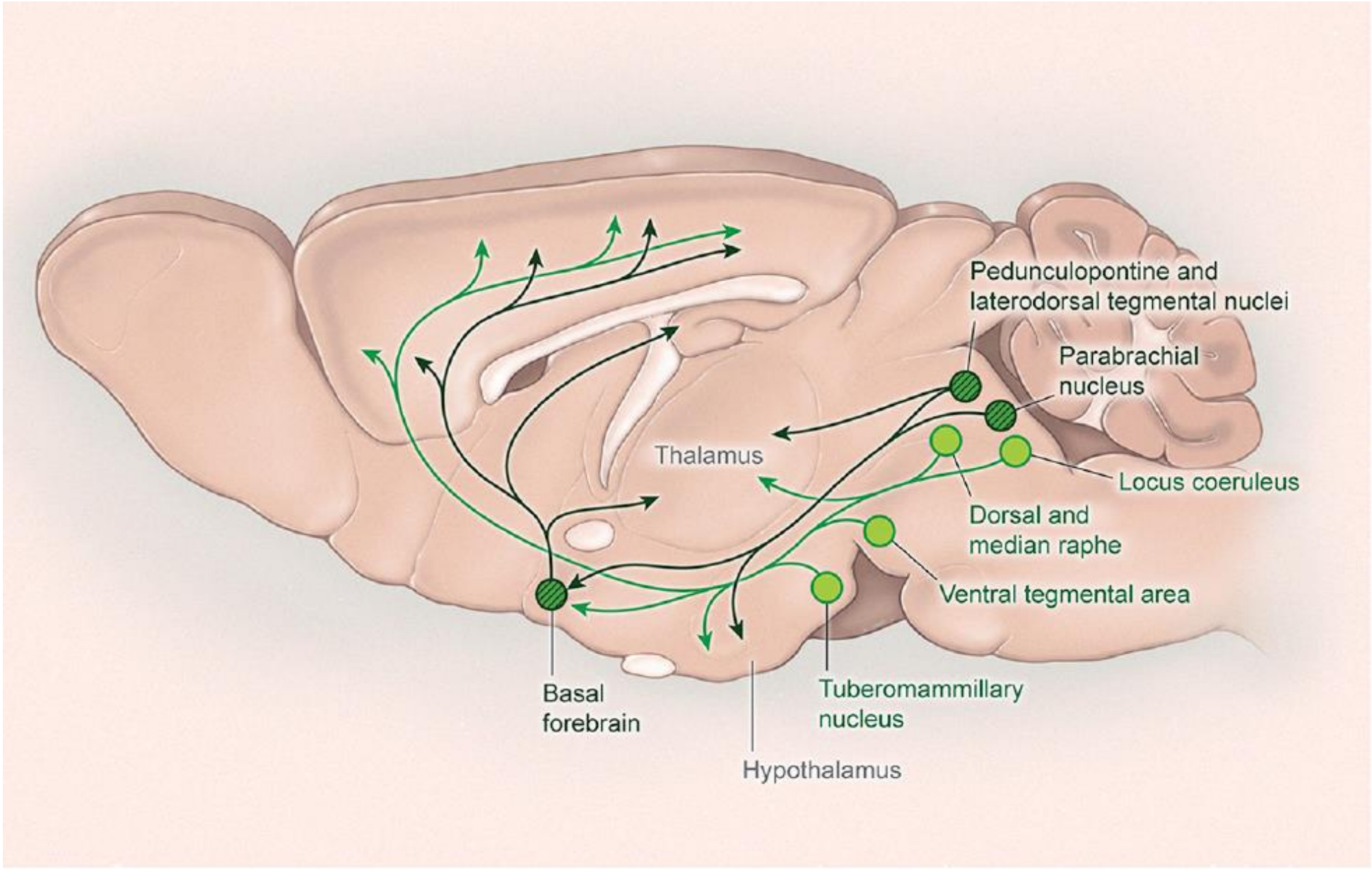
- Vastly disparate networks with vastly disparate functions
- Network activity may be intrinsic to a subsystem, integrated, or communicative (e.g., slow oscillation, spindles, long range integration from cortex to brainstem)
- Minimal overlap of fundamental oscillatory outputs
  - Spindles, heart rate, 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

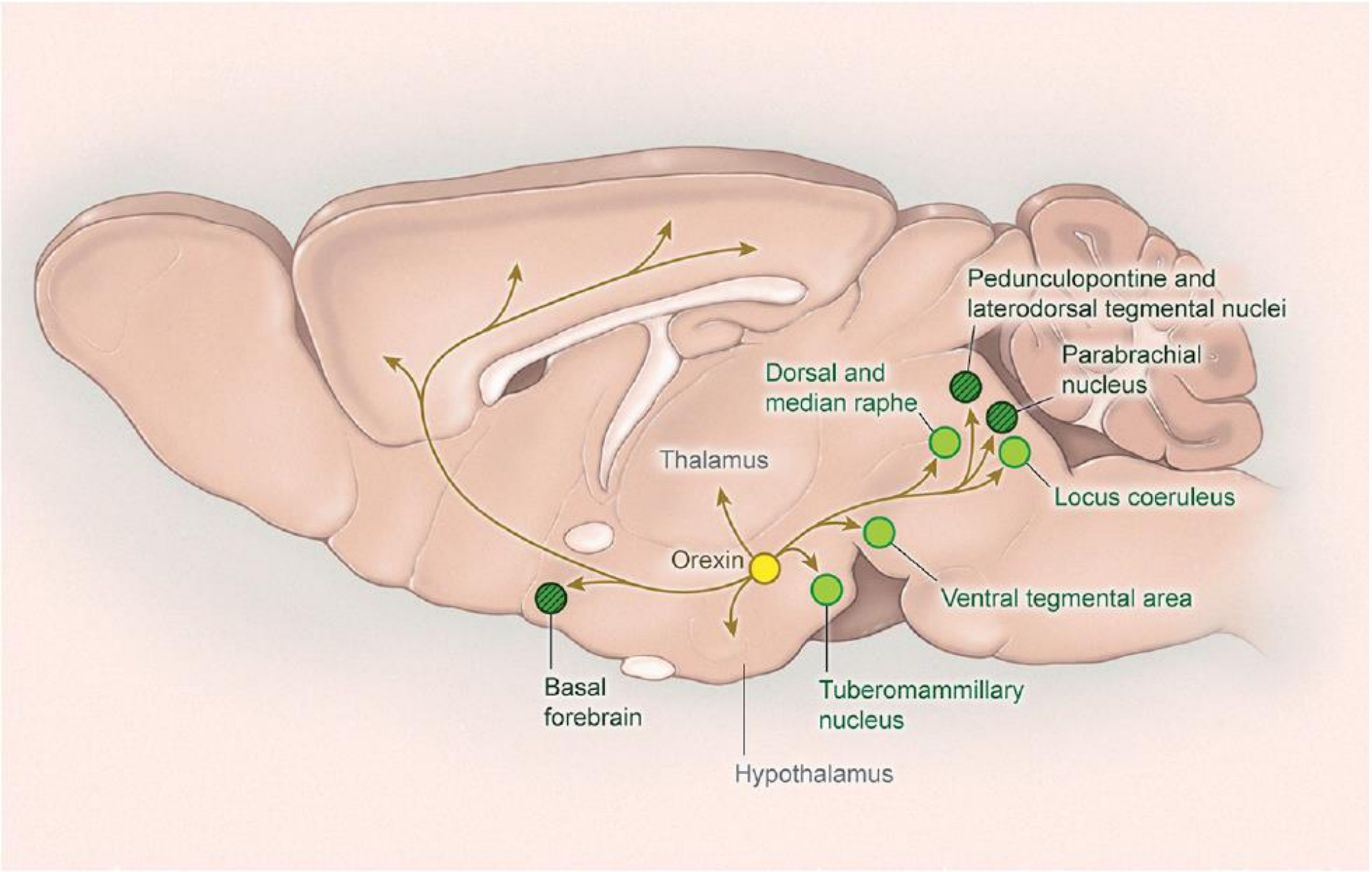
- Cortical
- Thalamocortical
- Intra-thalamic
- Brainstem
- Chemoreflex
- Baroreflex
- Central autonomic network
- REM-NREM
- Wake to sleep transition
- Arousal
- Respiratory generative
- Respiratory control
  - Rhythm
  - Airway
- Motor control
  - Periodic
  - Aperiodic
- Cardio-autonomic

Wake

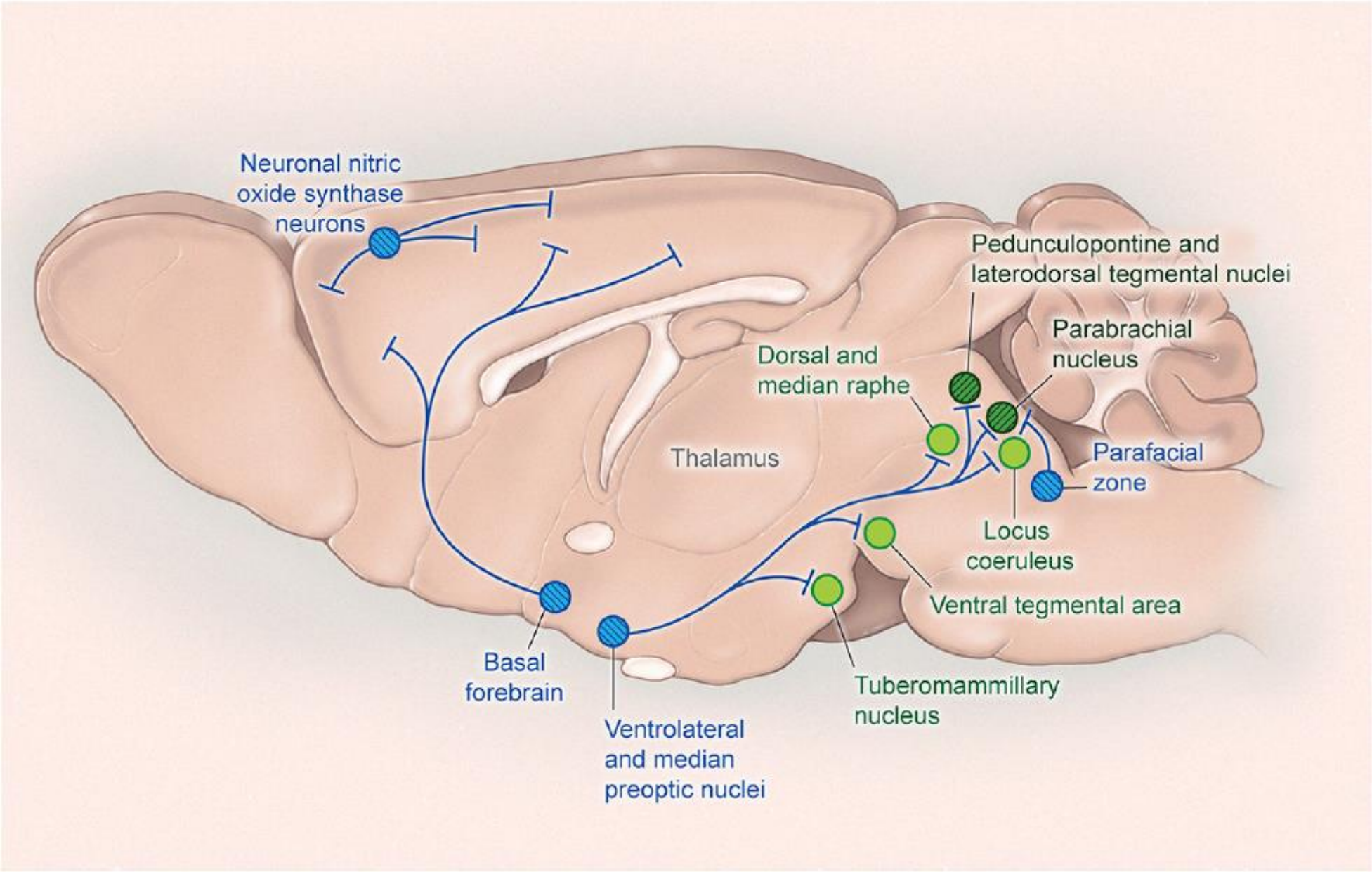
Neuron 201722;93: 747-765.



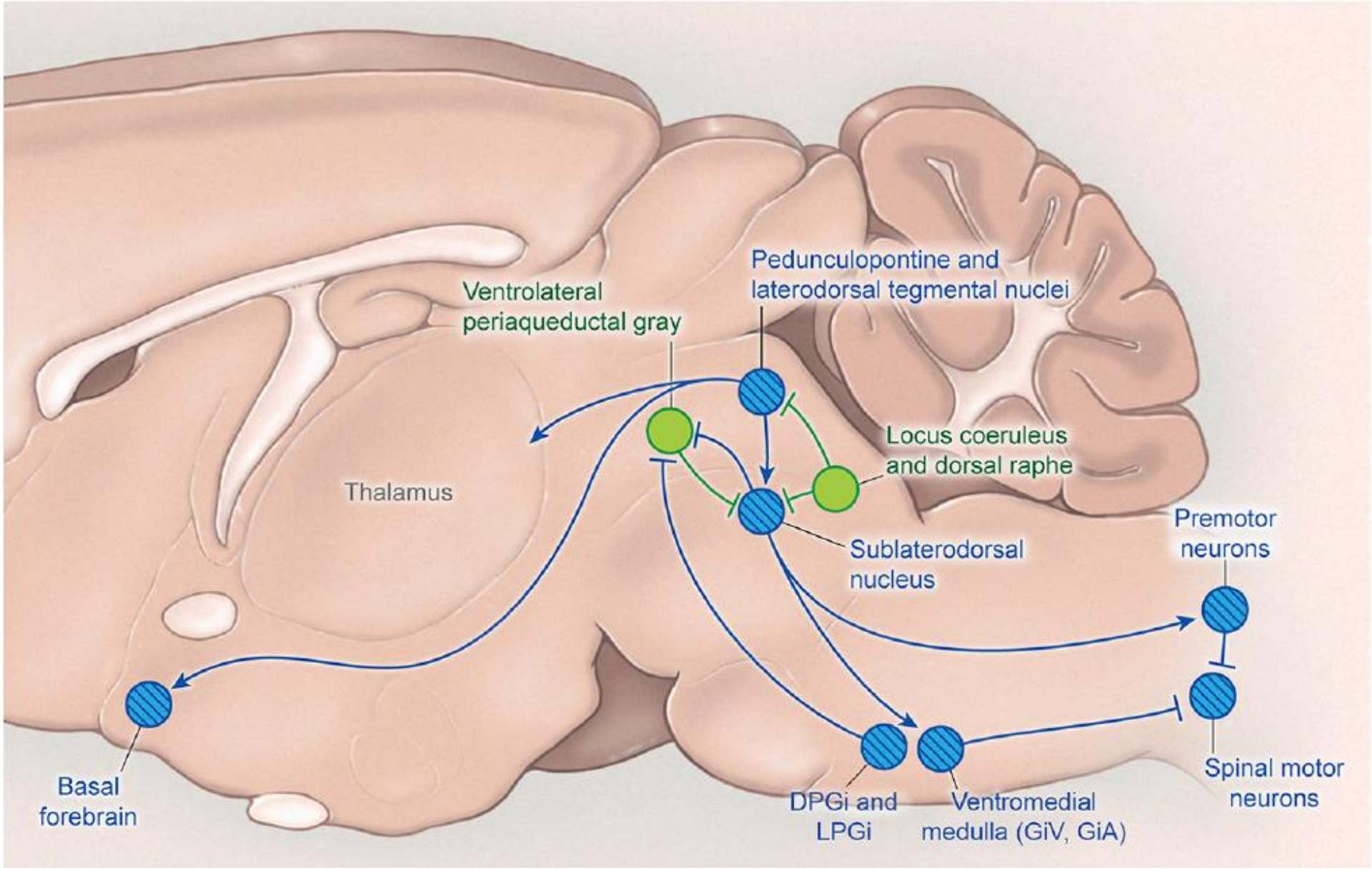
Orexin


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

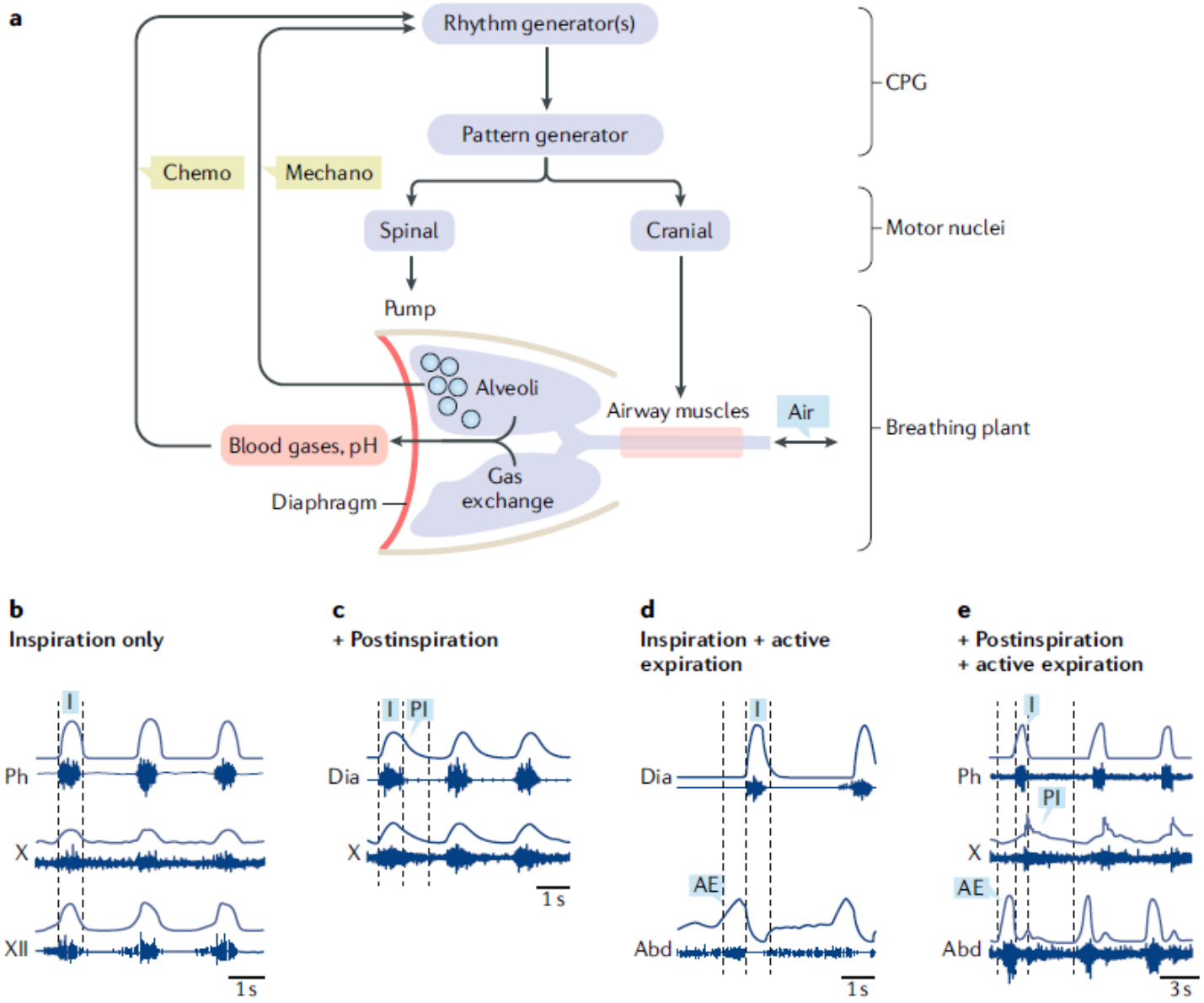

Ventrolateral
periaqueductal gray
Pedunculopontine and
laterodorsal tegmental nuclei
Locus coeruleus
and dorsal raphe
Thalamus
Sublaterodorsal
nucleus
Premotor
neurons
Basal
forebrain
DPGi and
LPGi
Ventromedial
medulla (GiV, GiA)
Spinal motor
neurons

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.

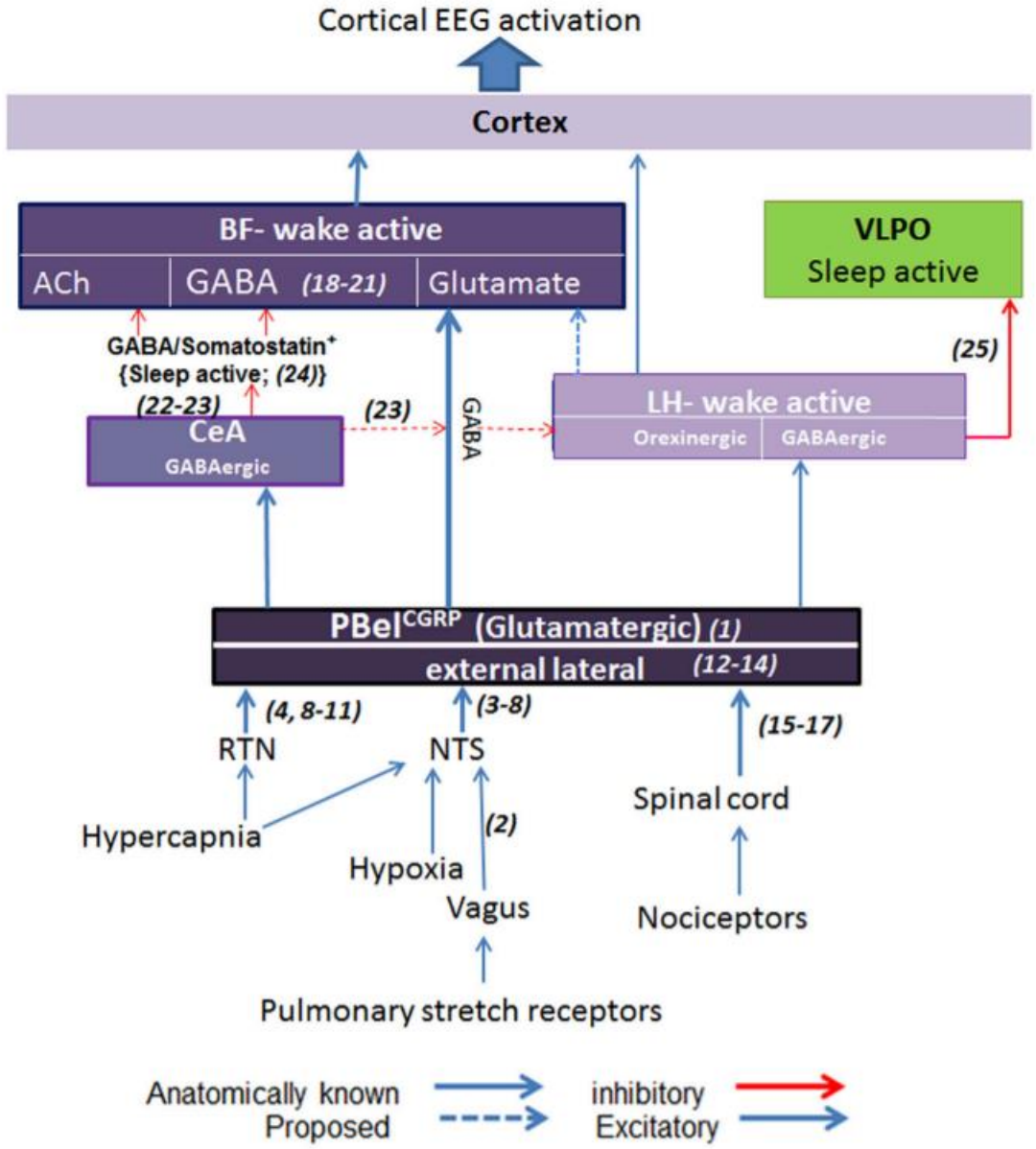
Respiratory Network

Nat Rev Neurosci 2018; 19:351-367



Hypercapnia

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



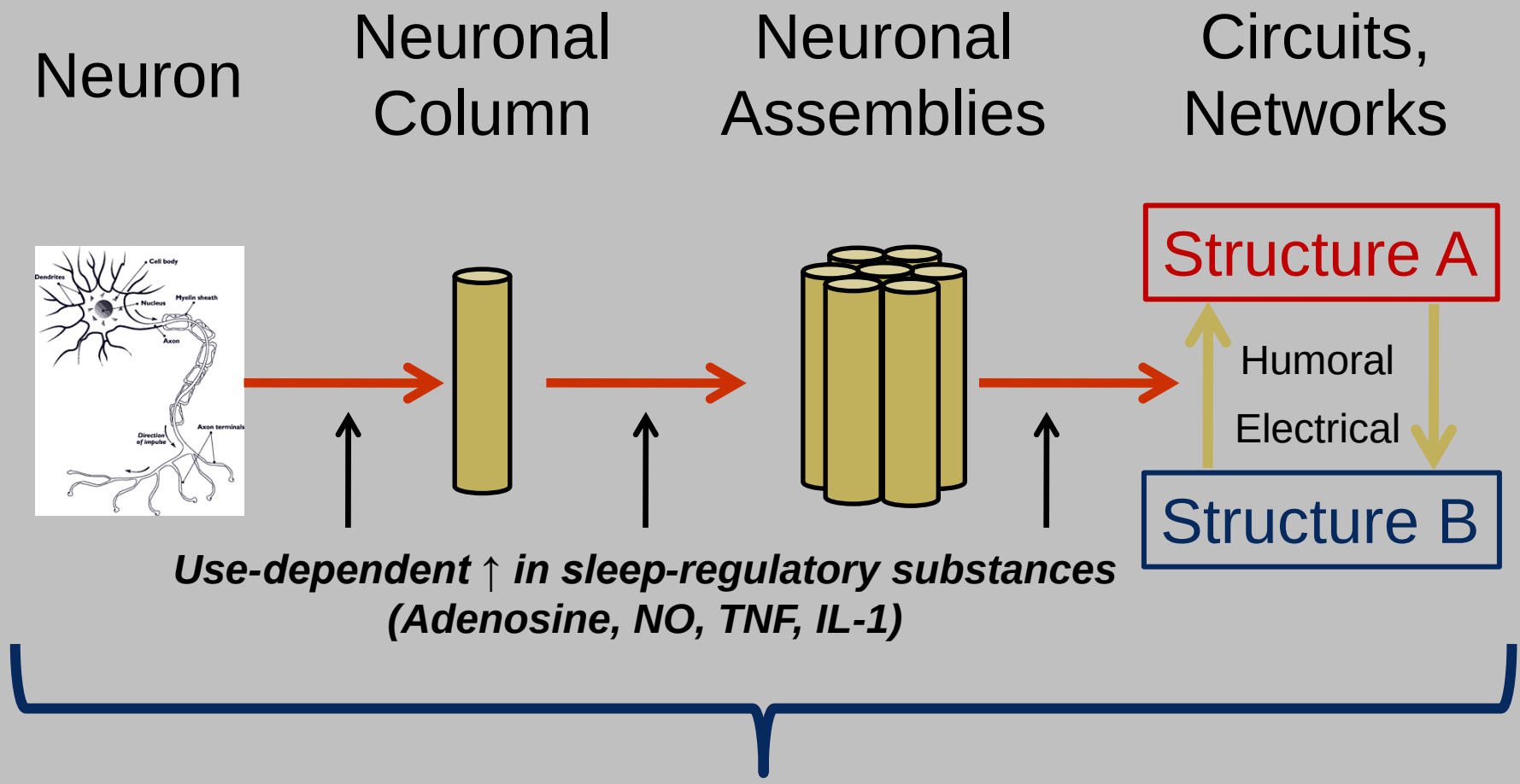
Respiratory network dysfunction

- 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

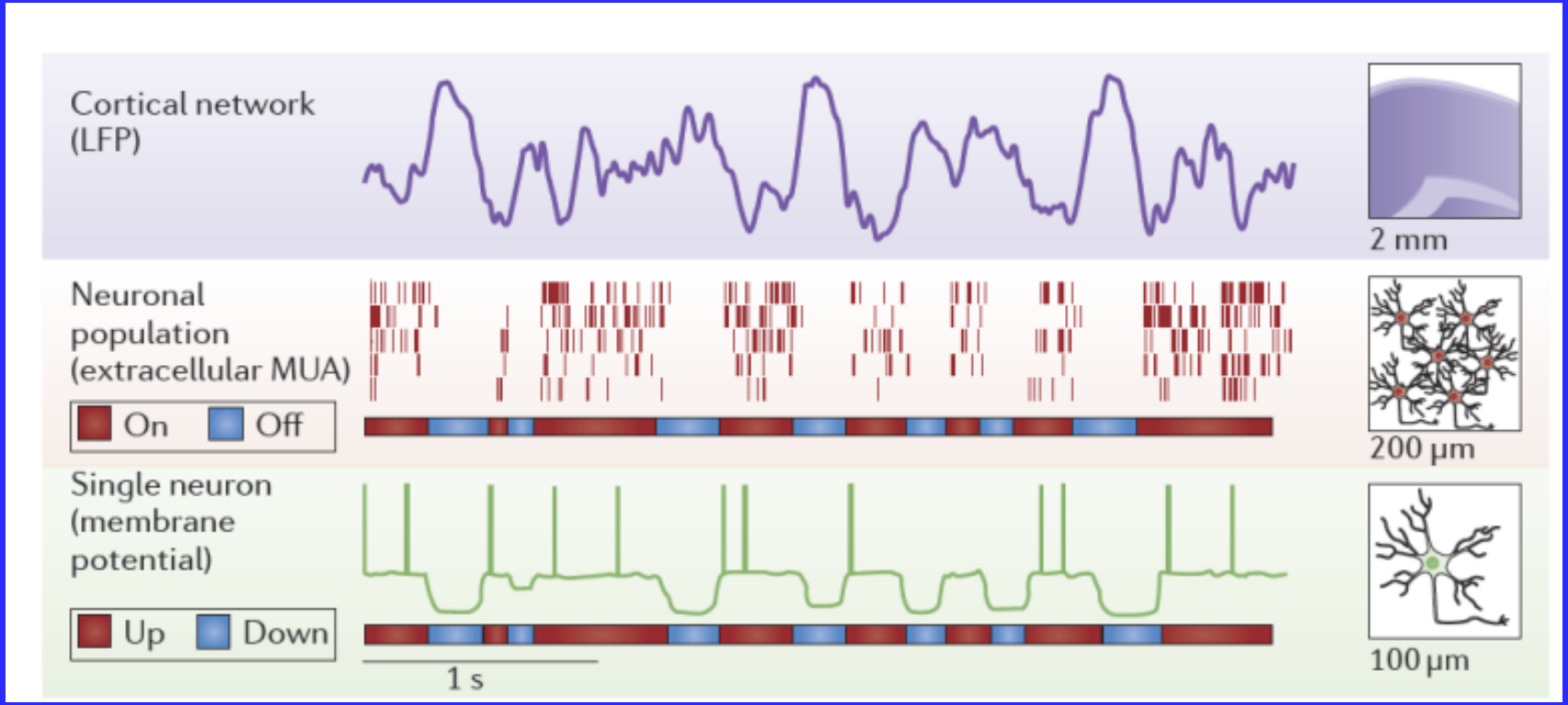
- No need to spend much time on this for a sleep medicine audience
- Thalamocortical cell conductance (including hyperpolarization activated spike), reticular thalamic nucleus, spindles, 1-4Hz delta
- Spindles could be analogous to a 5G cell network
- The SO synchronizes and aggregates spindles, which 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

“Local sleep” and systemic sleep

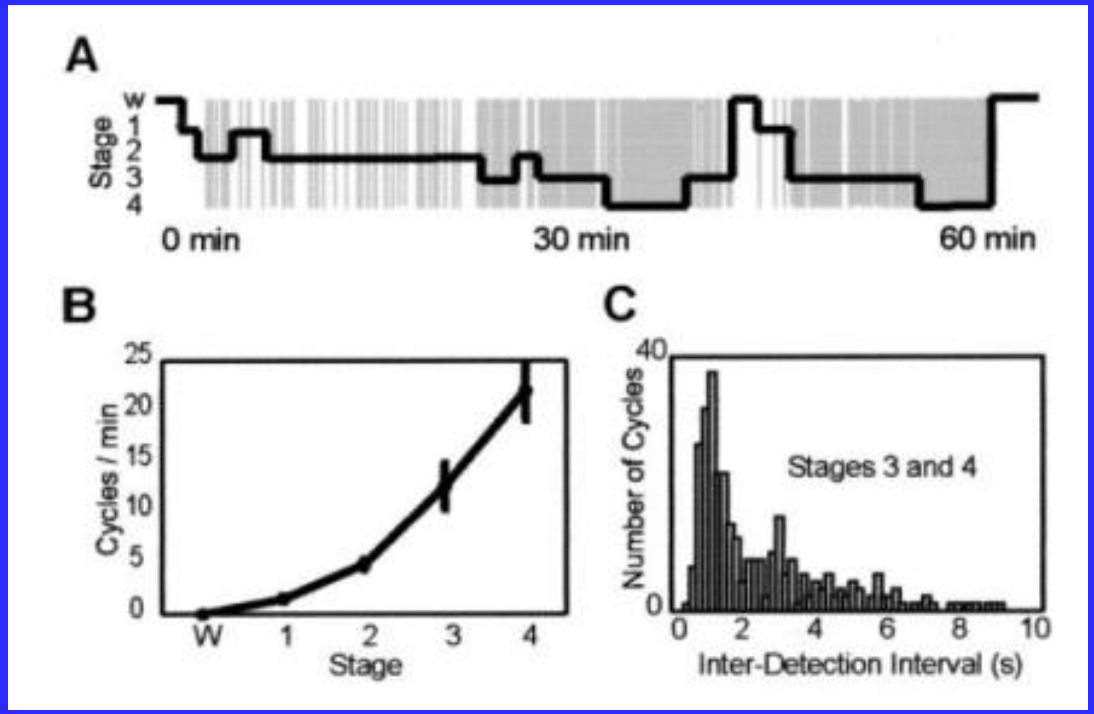


Krueger et al., *Nature Reviews Neuroscience* 2008; 9:910-919

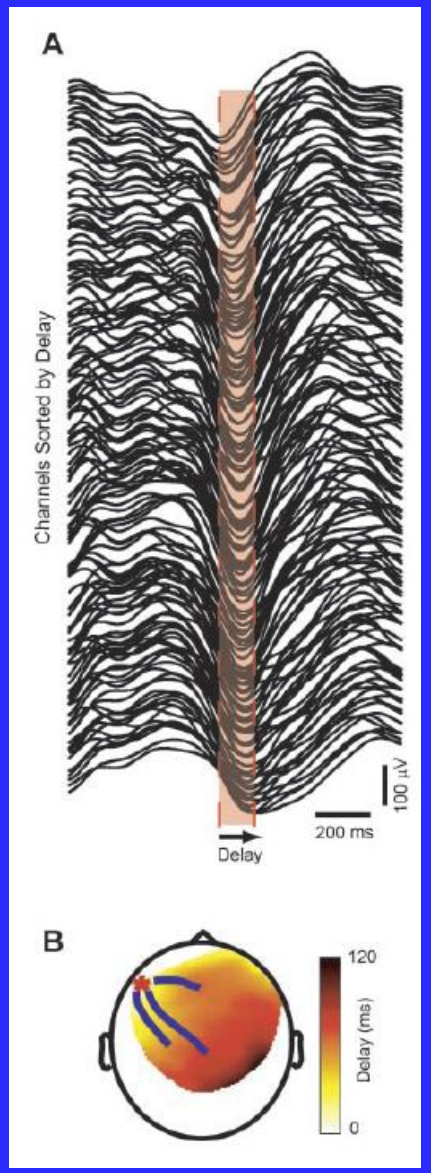
The “up” and “down” (on/off) states of the cerebral cortex. It permeates the whole brain.

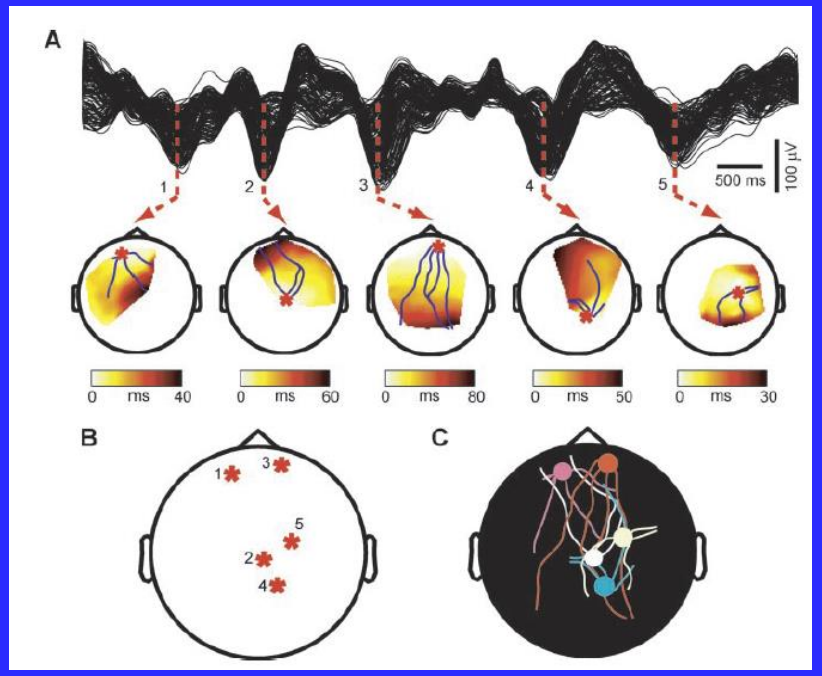


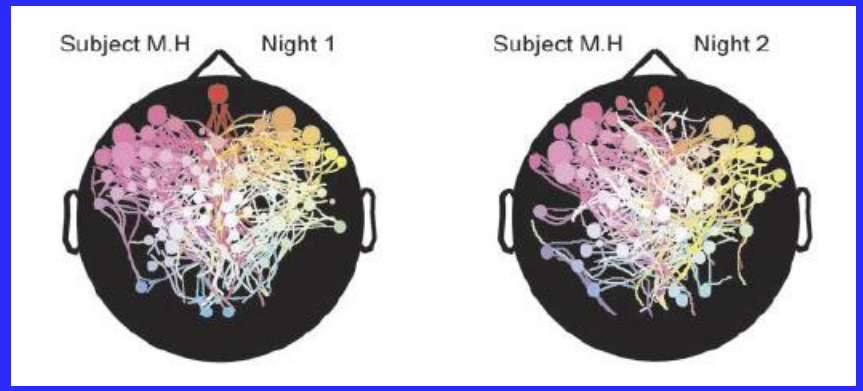
The Slow Oscillation (SO) builds in frequency and spatial extent as sleep starts and deepens. Below-high within individual stability.



More SO traveling wave characteristic

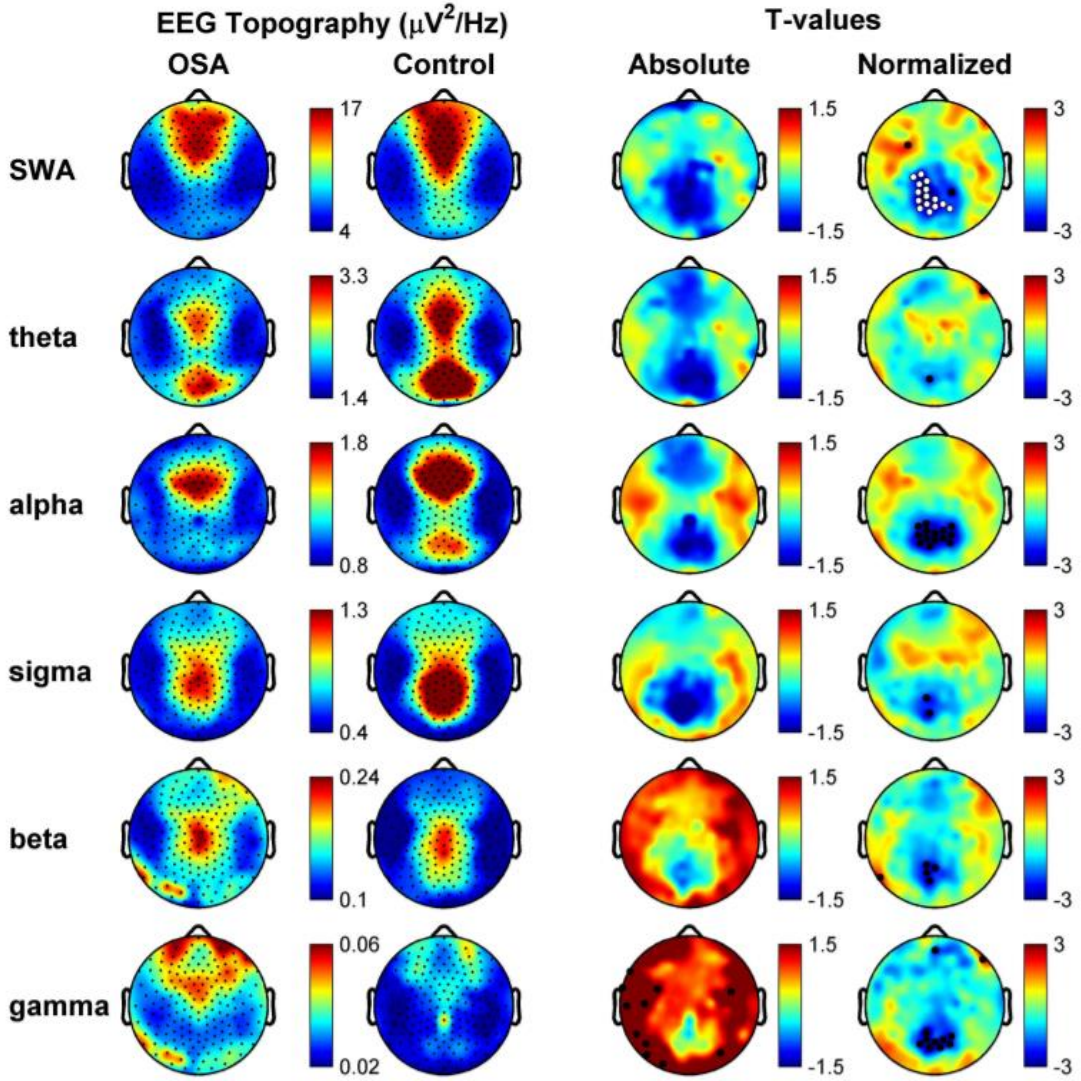


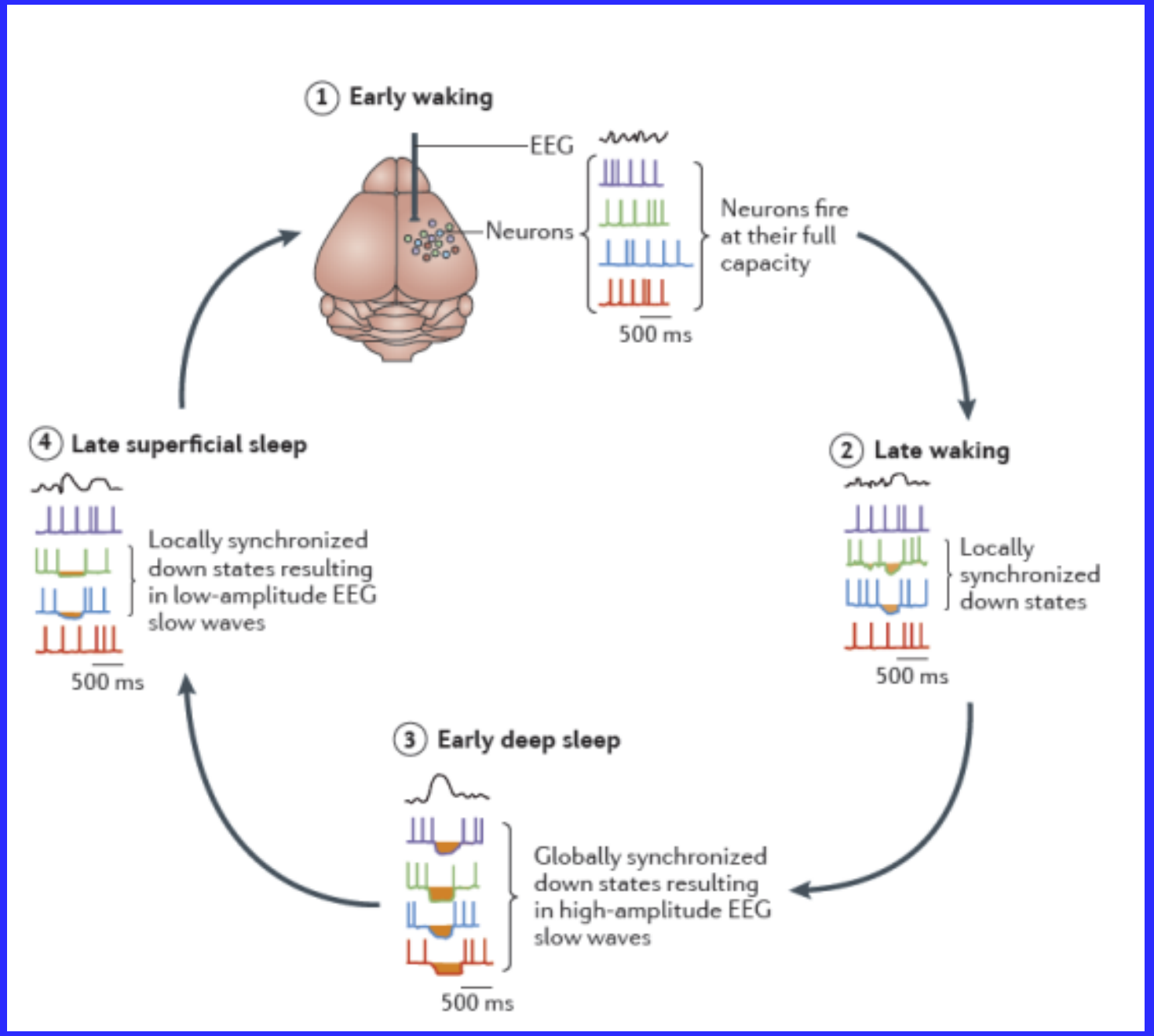




High density EEG polysomnography

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




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

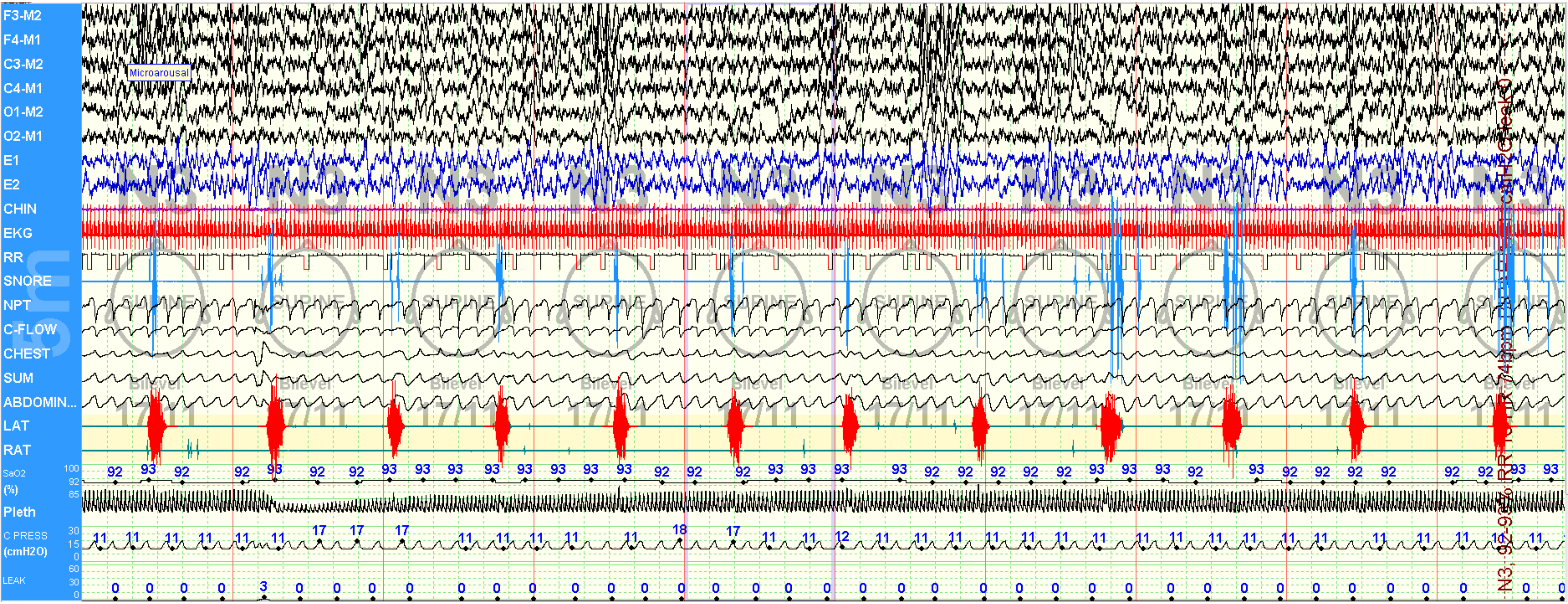
- Through targeted ablation in rats, a potential role for corticospinal, cerebellorubro-spinal, and hypothalamic A11 dopaminergic systems in the development of RLS-like movements during sleep. Targeted lesions in select basal ganglia structures revealed a major role for nigrostriatal dopamine, the striatum, 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

Central autonomic network

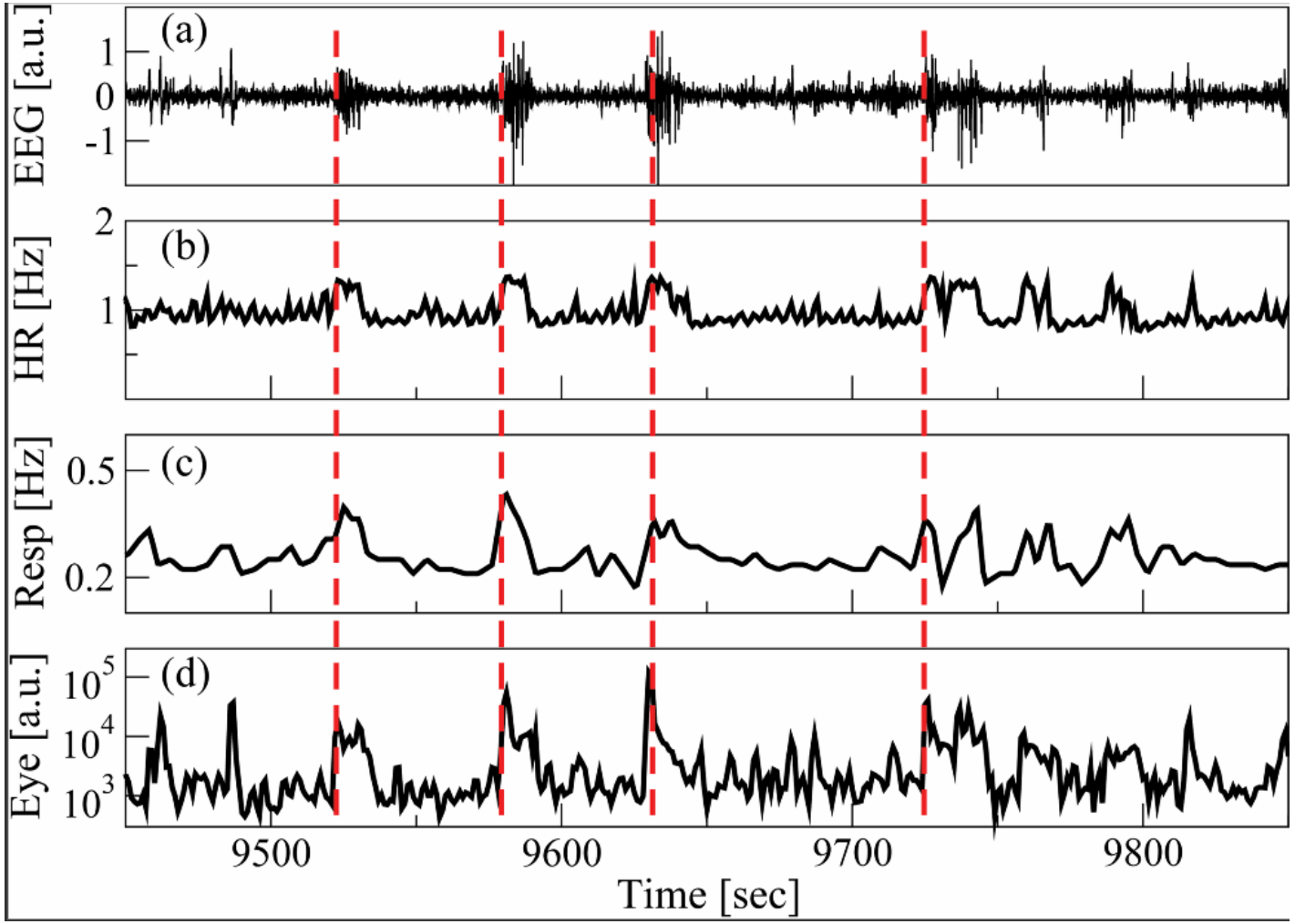
- Components include insular cortex, ventromedial prefrontal cortex and anterior cingulate (Cortical control of the autonomic nervous system. Exp Physiol 2014;99:326-331)
- Tight functional links to amygdala, hypothalamic paraventricular nucleus, parabrachial nucleus
- Reliably activated by pain, visceral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

How can we measure the network health of sleep?

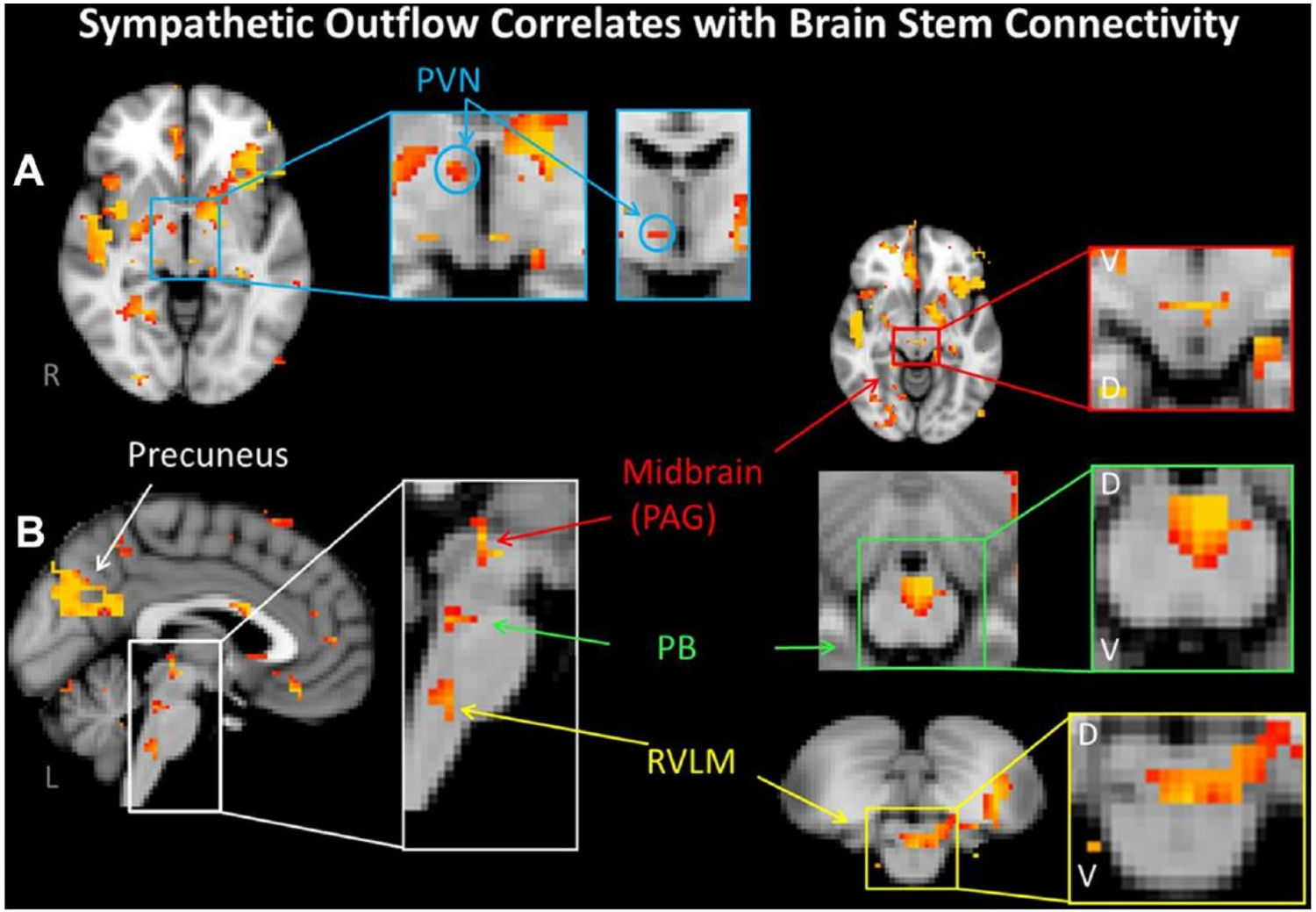
Technologies and approaches to measure sleep networks

- 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



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)