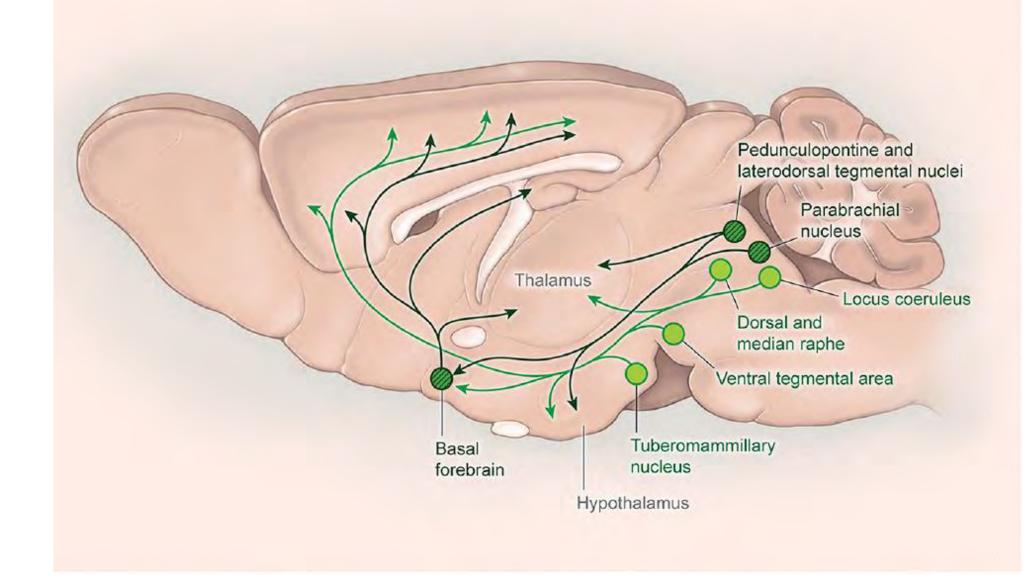
Sleep as a Network State (Part II)

Robert Joseph Thomas, M.D.

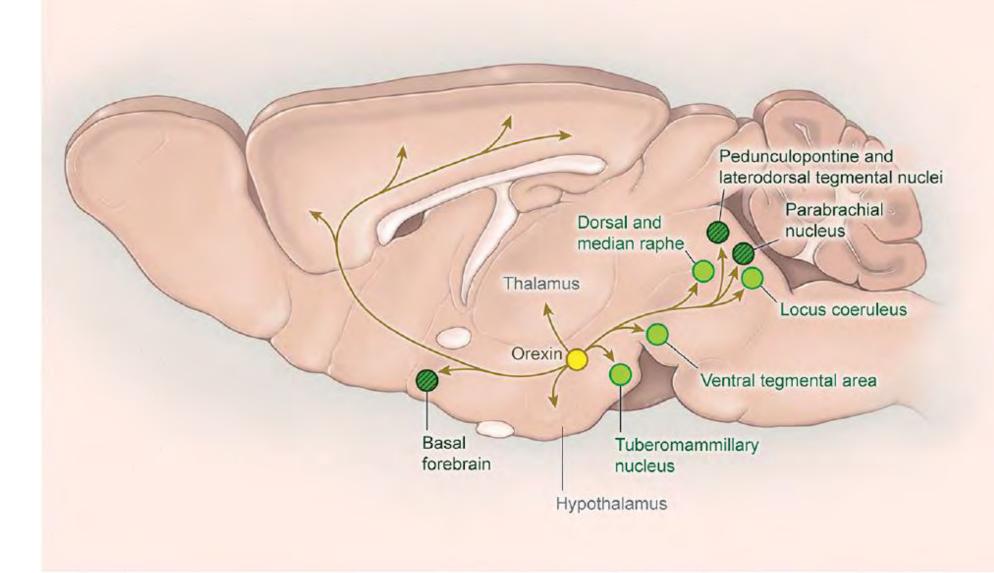
Beth Israel Deaconess Medical Center, Boston, MA, USA

Wake

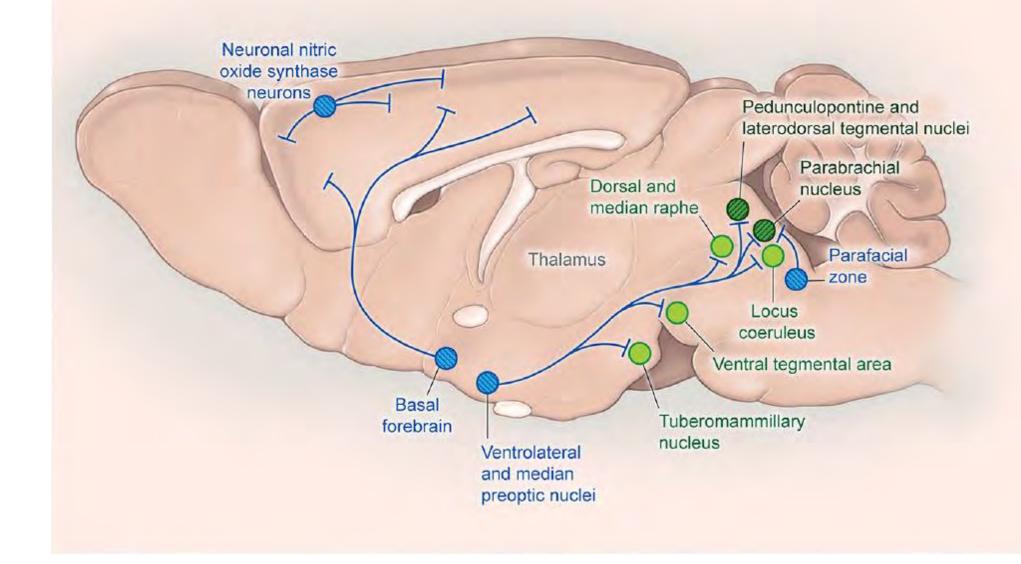
Neuron 201722;93: 747-765.



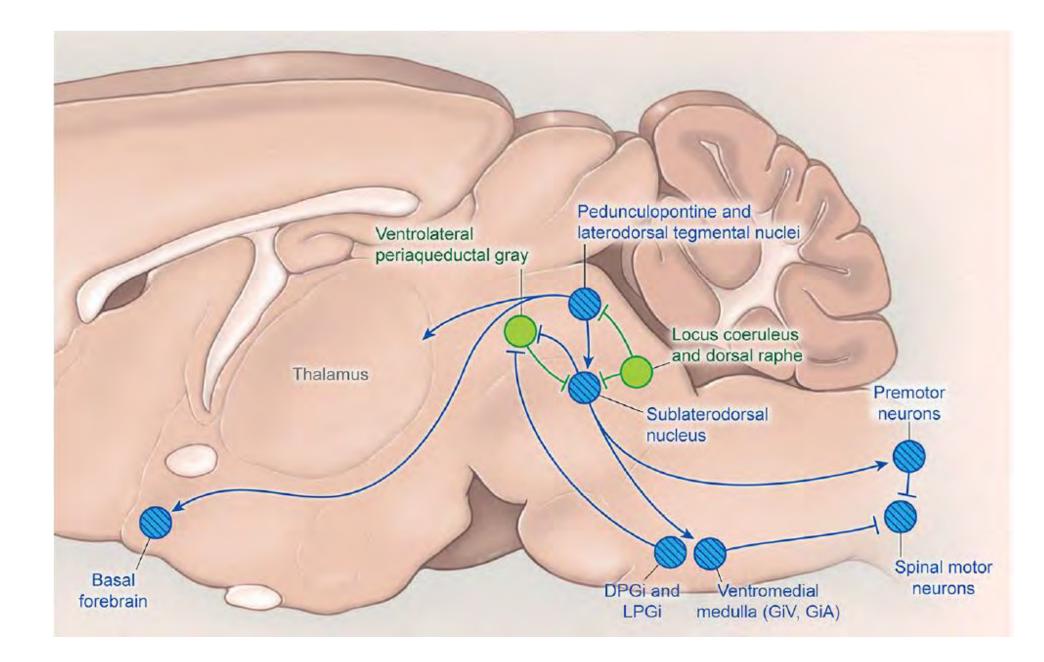
Orexin



NREM







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

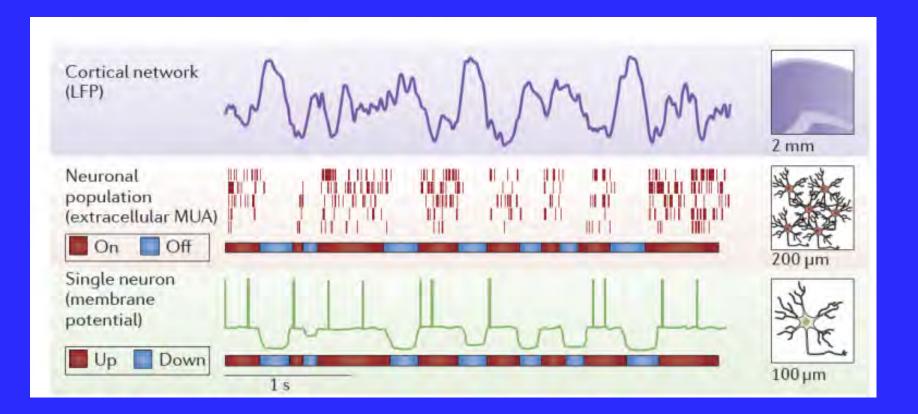
Network breakdown

- 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

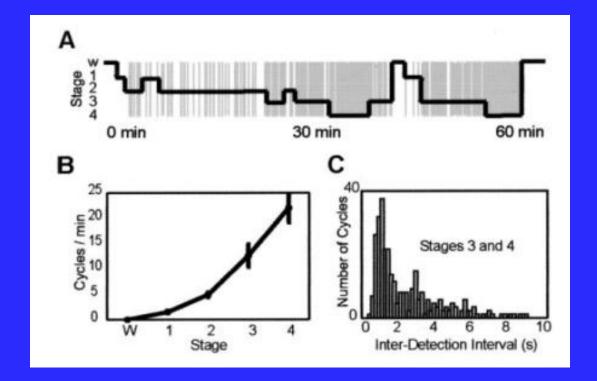
Network breakdown

- 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.



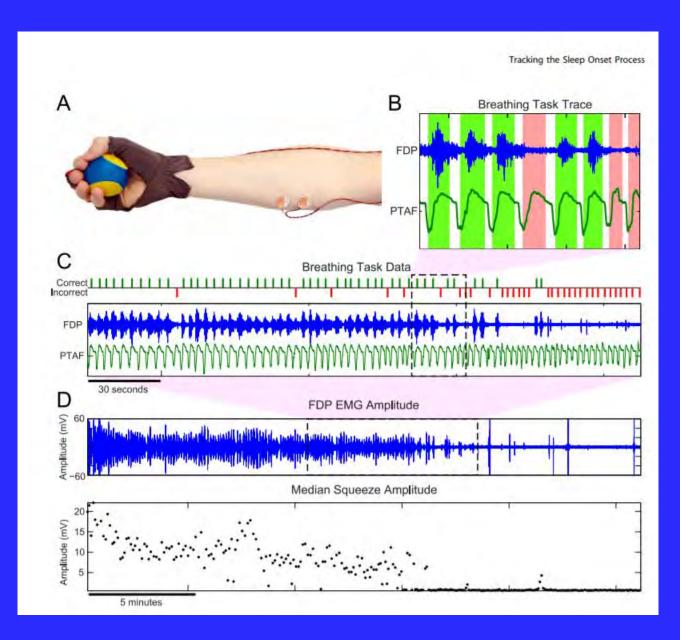
The Slow Oscillation (SO) builds in frequency and spatial extent as sleep starts and deepens. Below-high within individual stability.



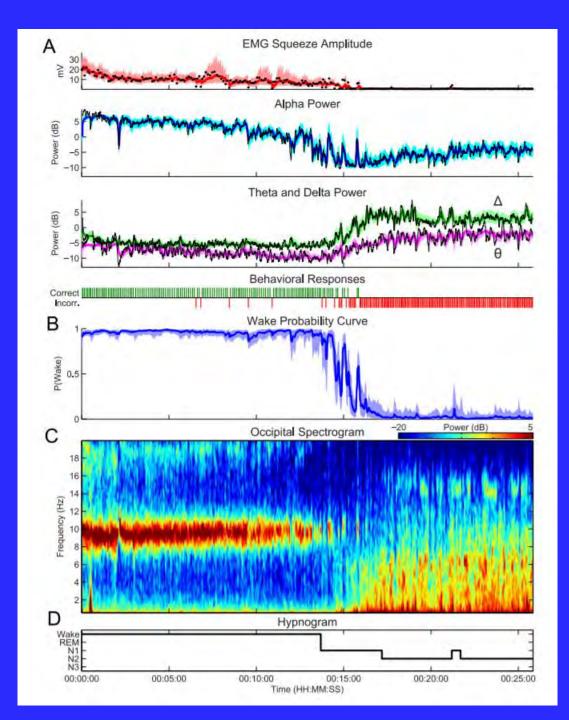
Consequences of the time of night distribution of the SO glue

- 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)

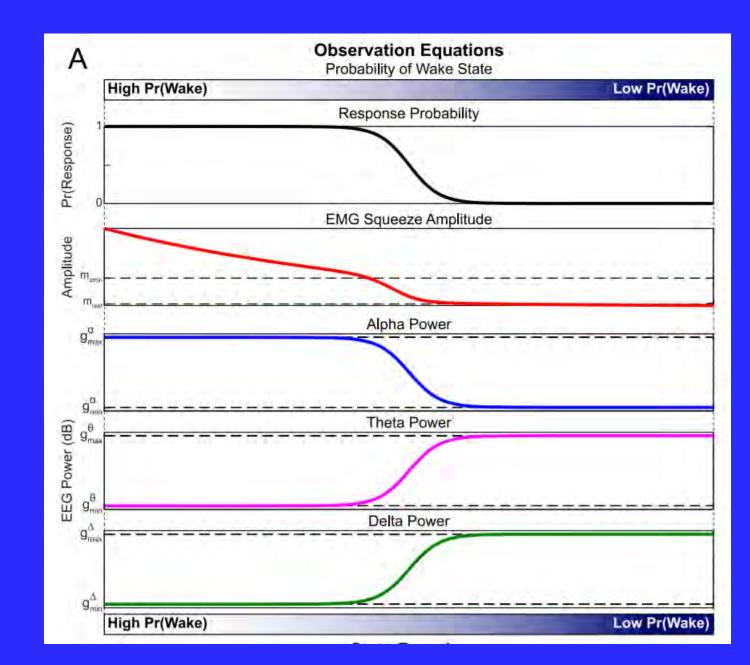
Sleep Onset



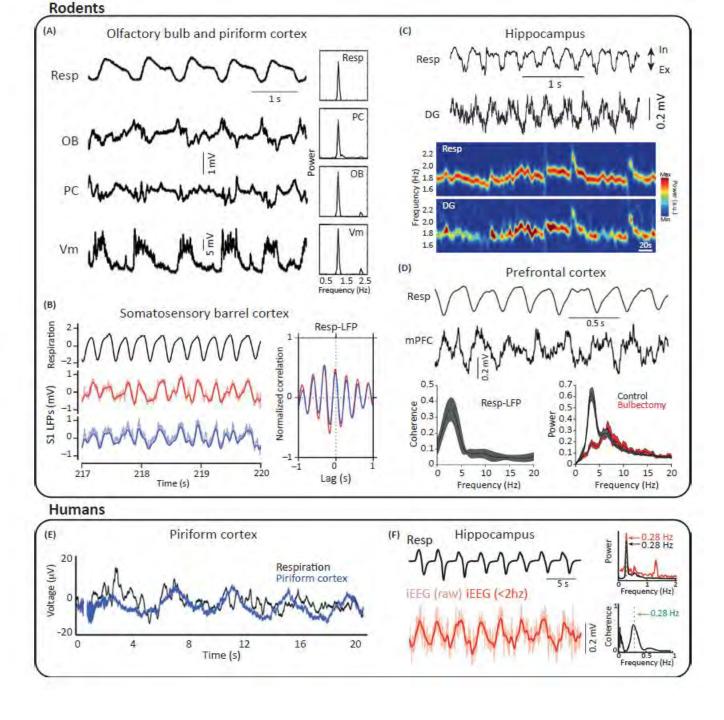
Sleep Onset



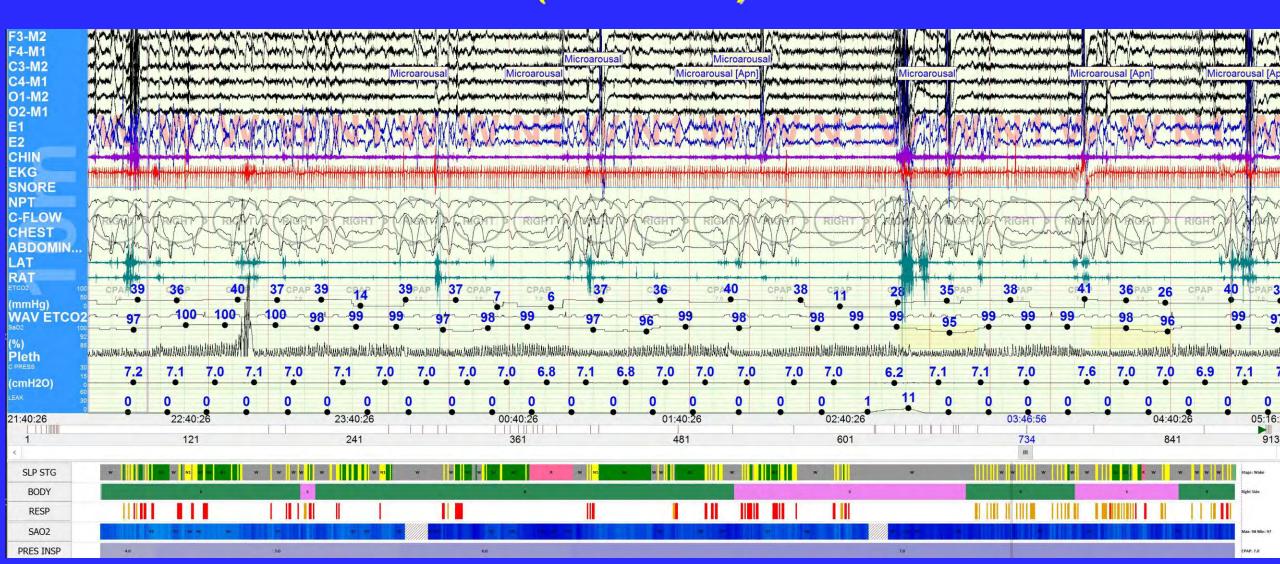
Sleep Onset



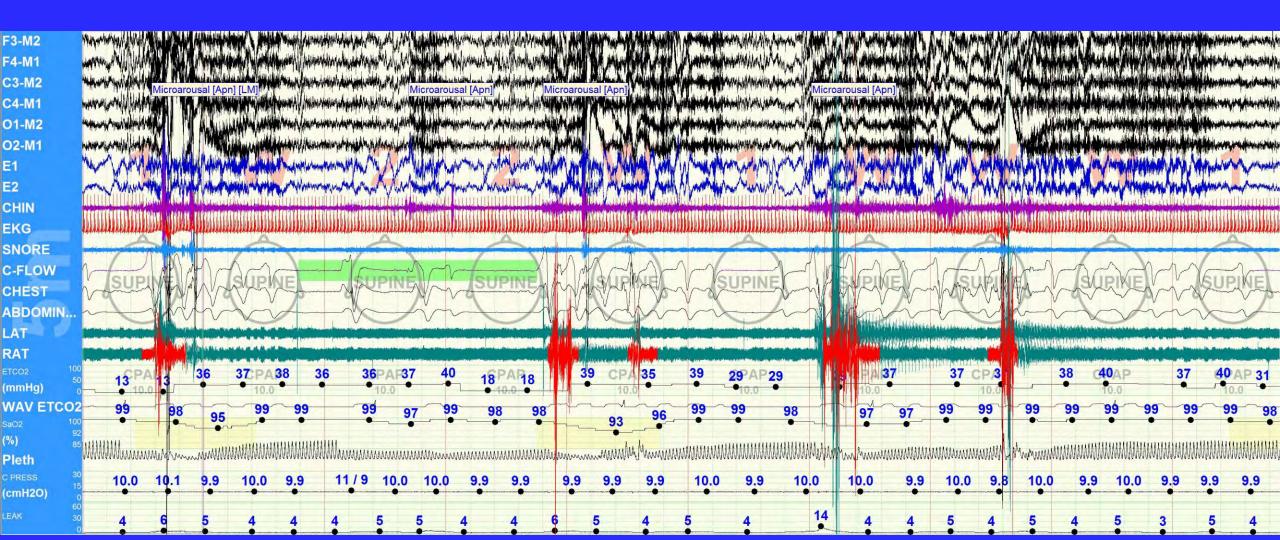
Respiration-Entrained Brain Rhythms Are Global but Often Overlooked. Trend Neurosci 2018;41:186-197.



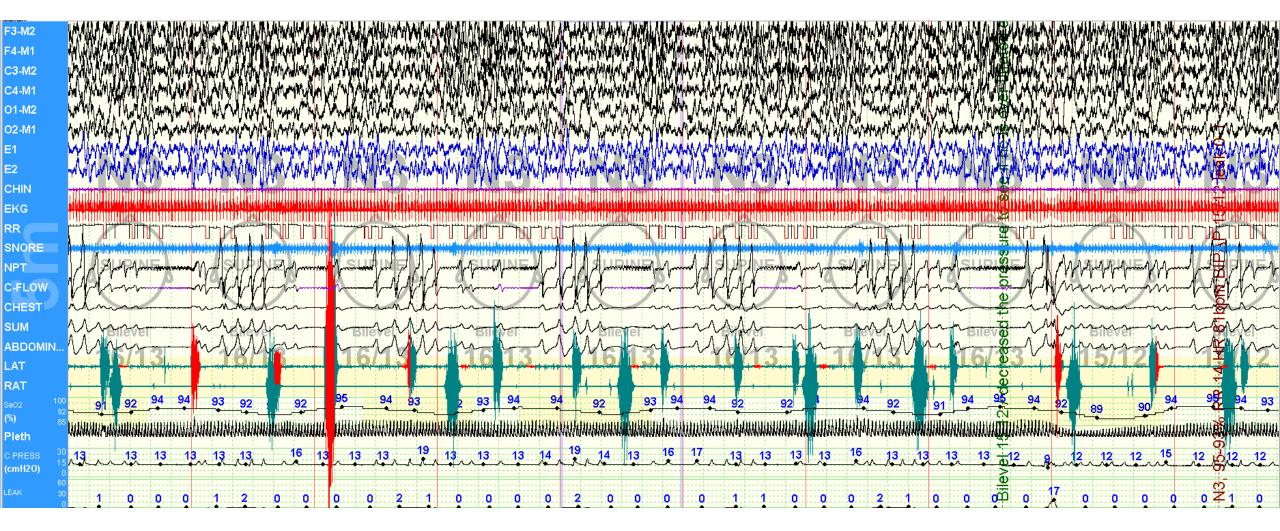
Amplified wake-sleep transitional instability (AWSTI)



AWSTI



Alternating PLMS +variable network coupling



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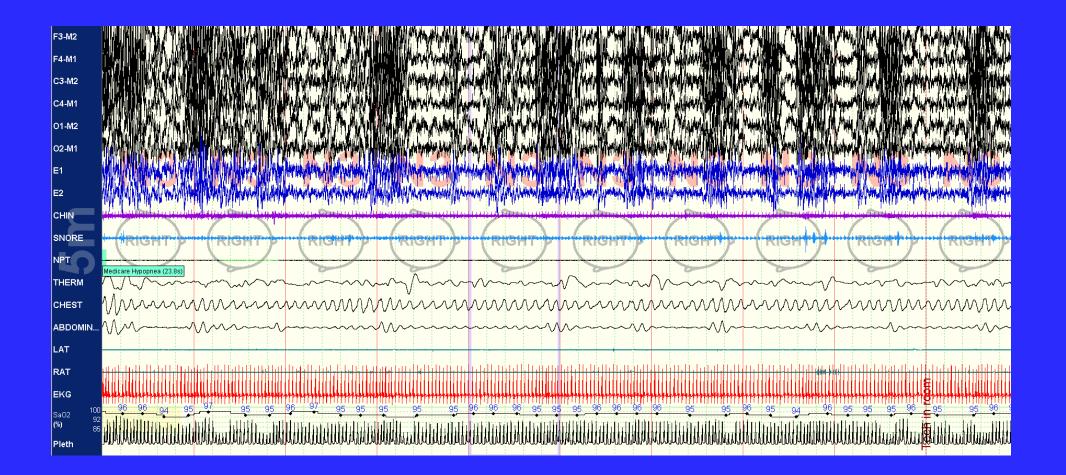
Cortico-motor network

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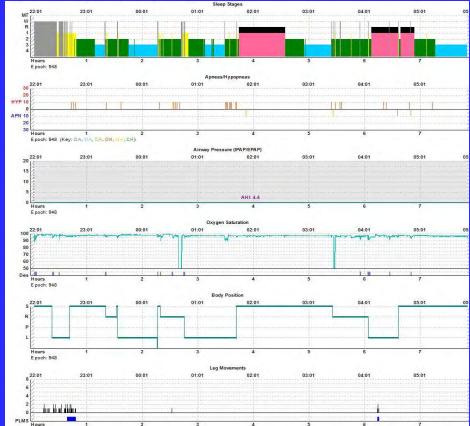
Cortico-motor network

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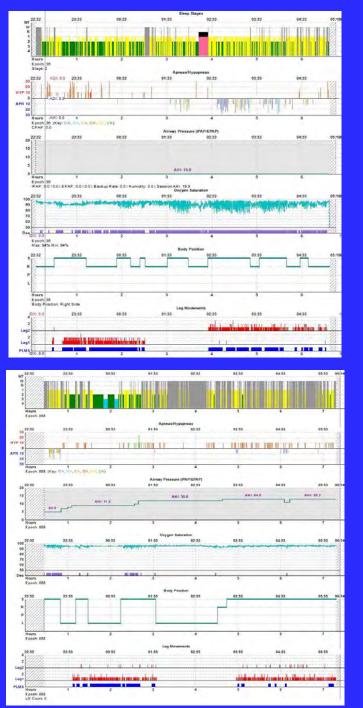
N3 CAP (5-minute)





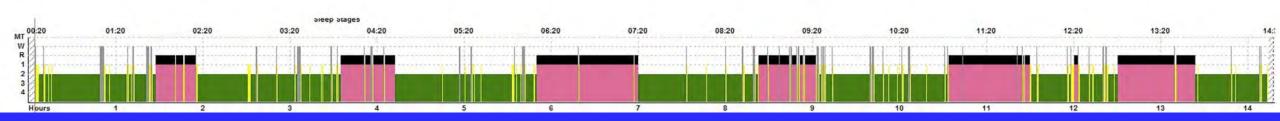


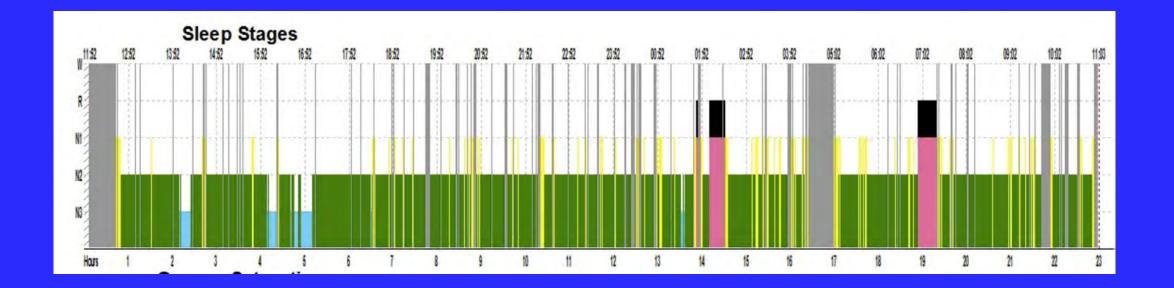
Network success



Network failure!

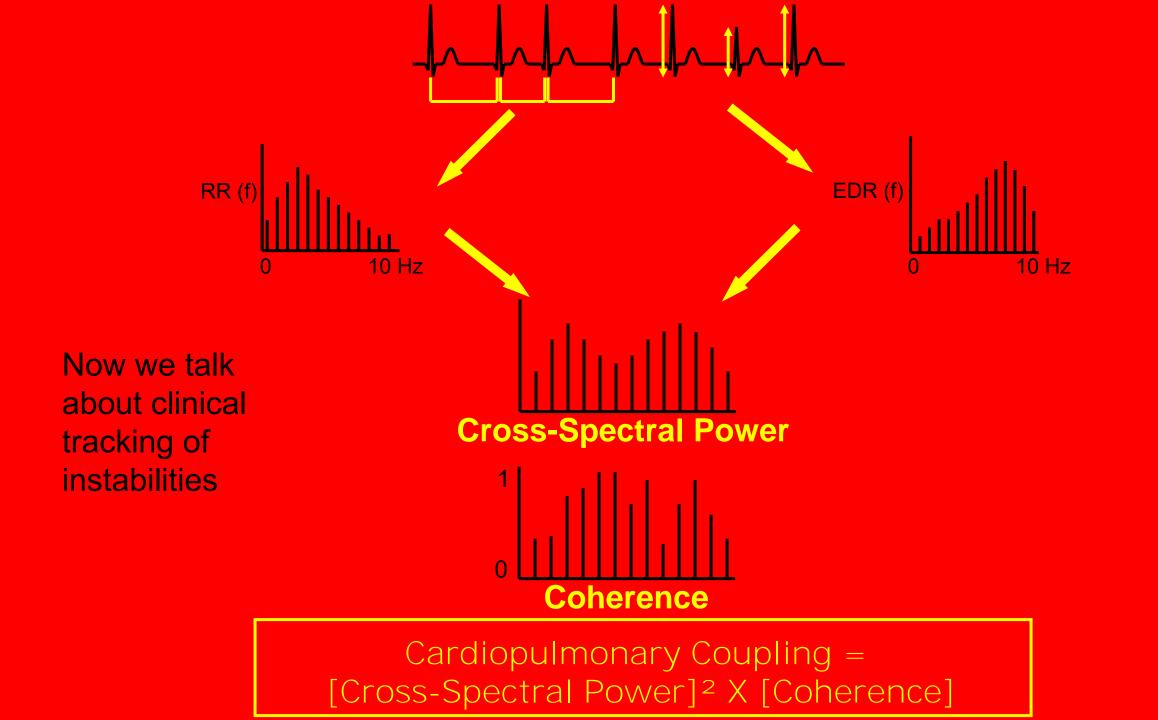
Idiopathic hypersomnia: network-off failure



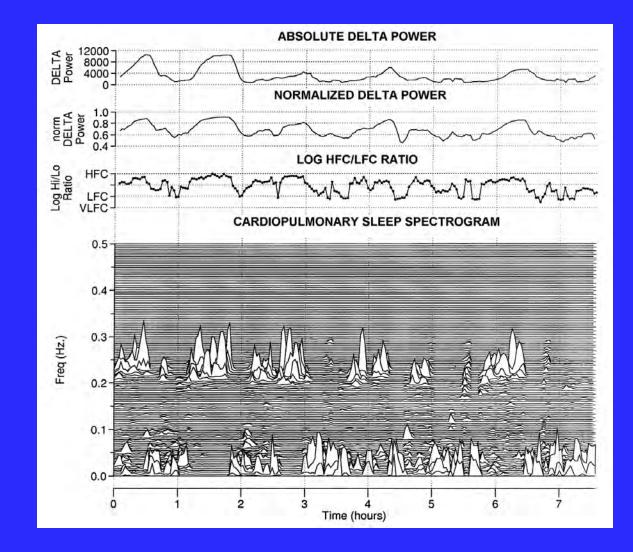


A speculative word on idiopathic hypersomnia

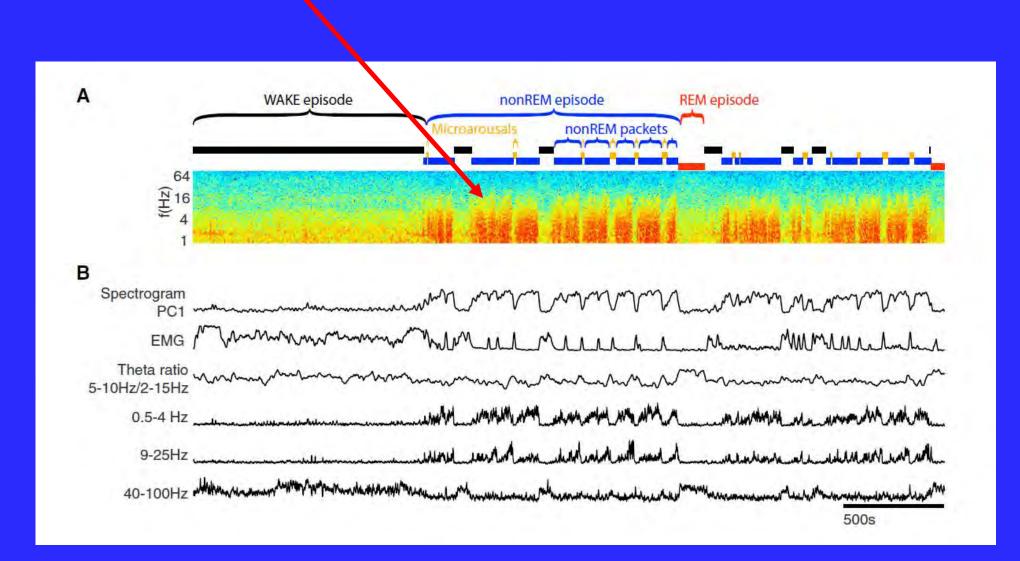
- Relevant to all hypersomnias with substantial sleep inertia
- A network transition disorder
- Pathological persistence of sleep network = long sleep
- Pathological inability to switch off for wake network = sleep inertia
- Mixed sleep-wake network persistence = fog
- Stimulants do not work well due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



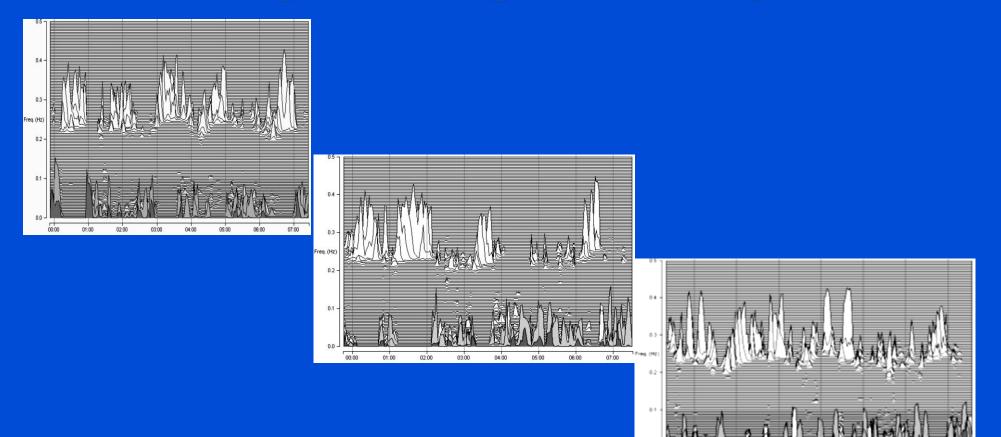
Slow wave power and ECG-spectrogram



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



Night-to-night stability

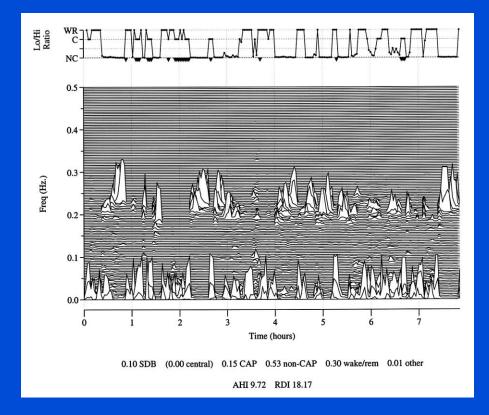


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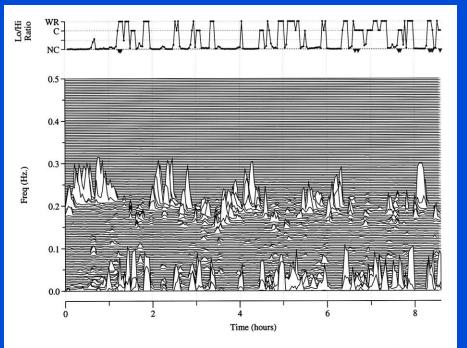
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Sleep deprivation recovery – increased HFC all across the night

Rested human



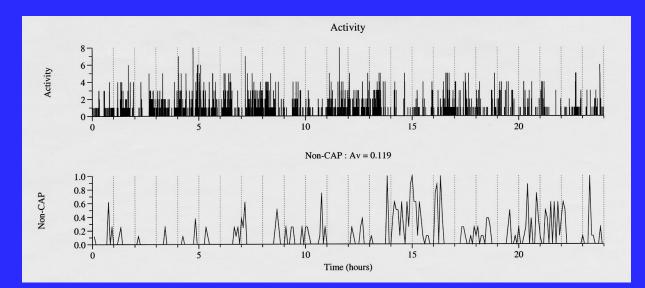
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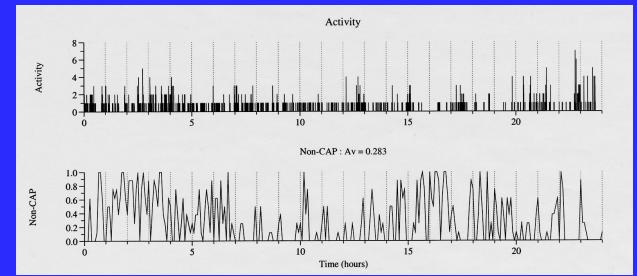
AHI 4.18 RDI 17.82

Blood pressure "dips" only during the periods of high frequency coupling



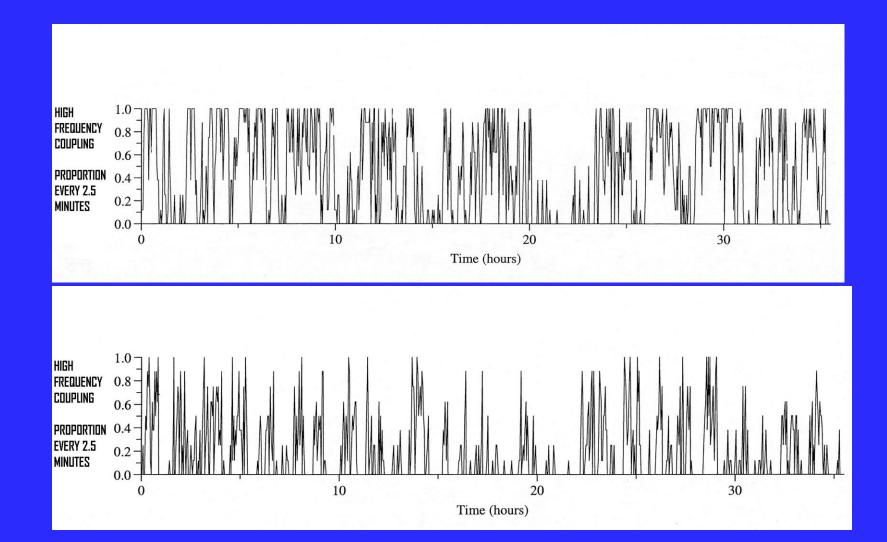
Benzodiazepines decrease slow wave but increases integrated stability (rat data)



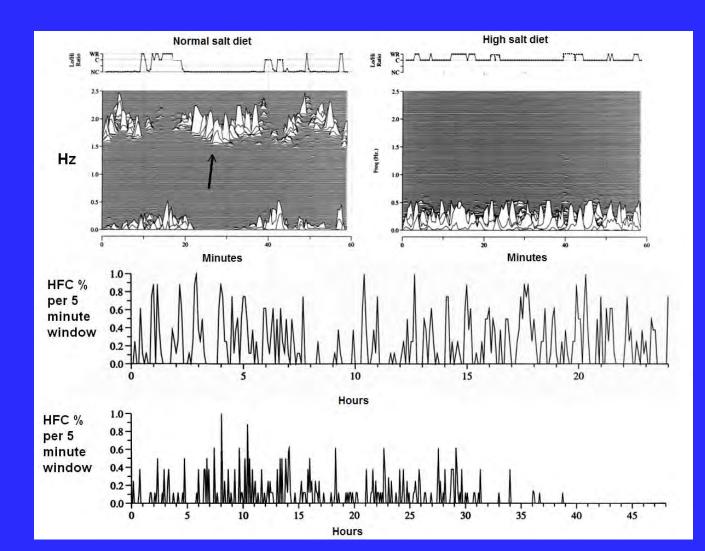


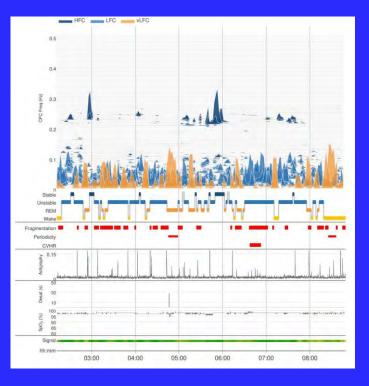
Lorazepam 0.9 mg/Kg/day

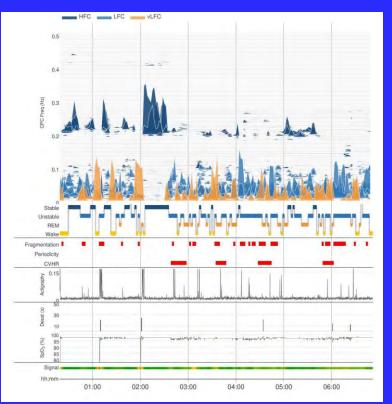
Sleep network fragmentation in Alzheimer's disease (transgenic mouse)



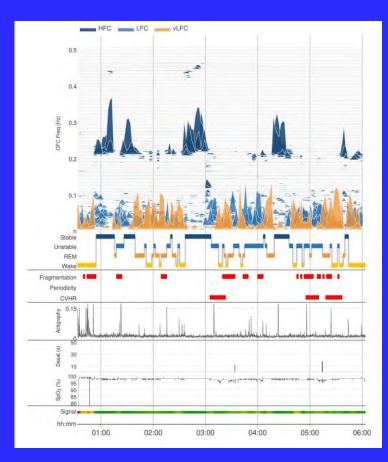
Sleep network fragmentation in heart failure







Sleep quality instability



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Sleep timing instability – pre/post lithium

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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 nonexistent in sleep practice