Biomarkers of Stable Sleep

Oscillatory Activity of the Brain Predicts Sound Sleep on Noisy Nights

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http://www.hms.harvard.edu/zzz

Before I begin…

- Toronto: experiences formed the motivation for these set of experiments
- What I learned:
  - Intra- and inter-individual differences in sleep depth
- Vulnerable populations
- Consequence (cognition and physiology)
- Opportunity for novelty regarding sleep depth and treatments

Outline

Background

- Introduction
- Sleep and cognition
- Noise perception during sleep

Questions to be addressed

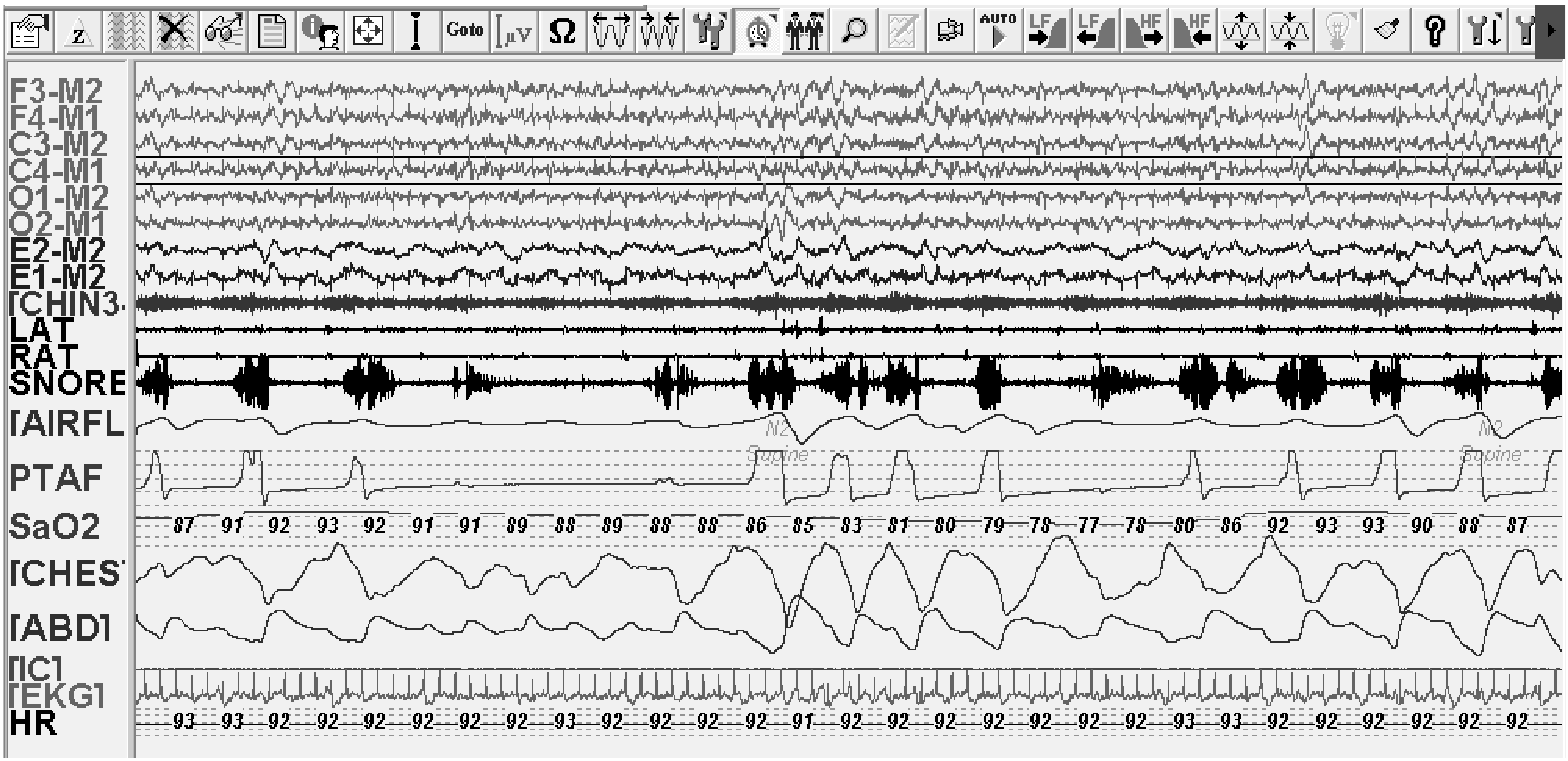
- Biological drivers of stable sleep
  - Sleep stages
  - Traits
  - States

Closing

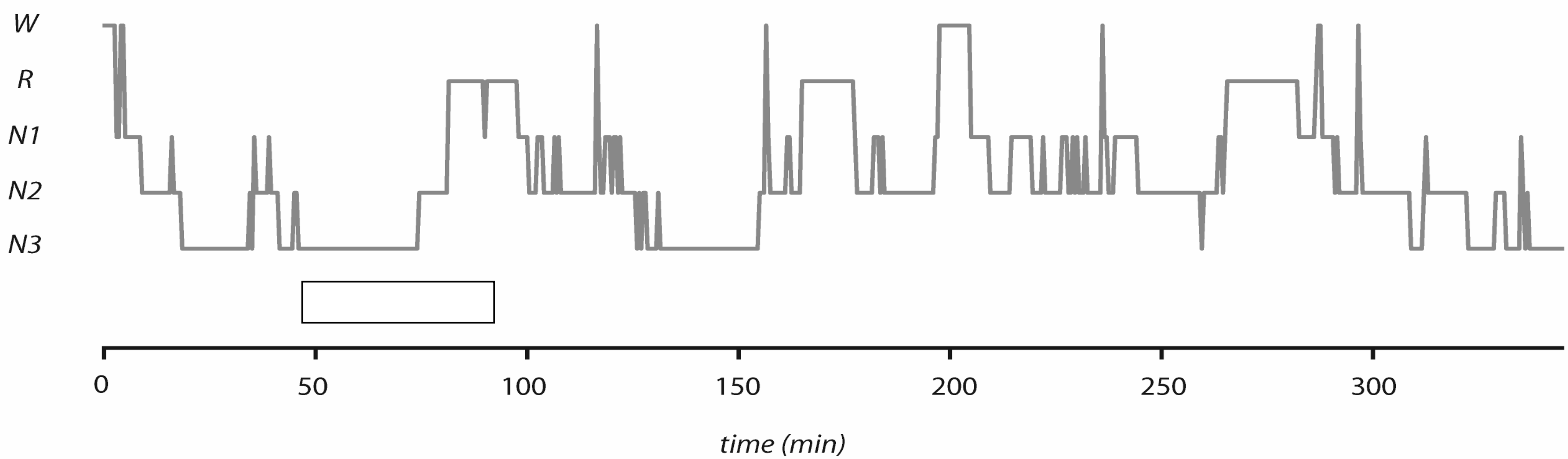
- Summary/Conclusions
- Future Directions
- Discussion

Sleep Lab

Sleep Disordered Breathing in AD



Sleep "Stages" (Hypnogram)



Raw EEG

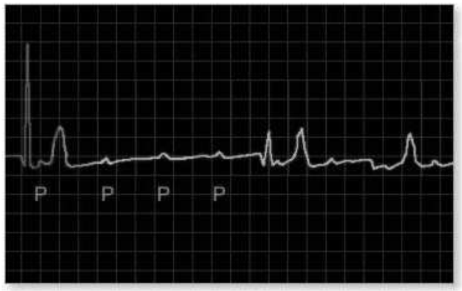
Predictors?

Can we employ features of human EEG in order to make insights (i.e., independent variables; predictors) about phenomena of the brain, mind, or disease (i.e., dependent variables; outcomes)?

Sleep and Cognition

- **How does sleep influence our waking experiences?**
  - e.g., memory enhancement; inferences
- **How do our waking experiences influence sleep?**
  - e.g., replay of events; slow-oscillations (is sleep local or global?)
- **How does cognition behave at the interface of sleep-wake?**
  - e.g., why don't we remember a phone call in the middle of the night?
- **What are the cognitive consequences of sleep disorders or sleep deprivation?**
- **What can sleep tell us about brain-based diseases or aging?**
- **How does the brain interact with the environment *during* sleep?**
  - e.g., sleep stability in noisy environments

Challenges to Sleep

Approaches to minimizing noise

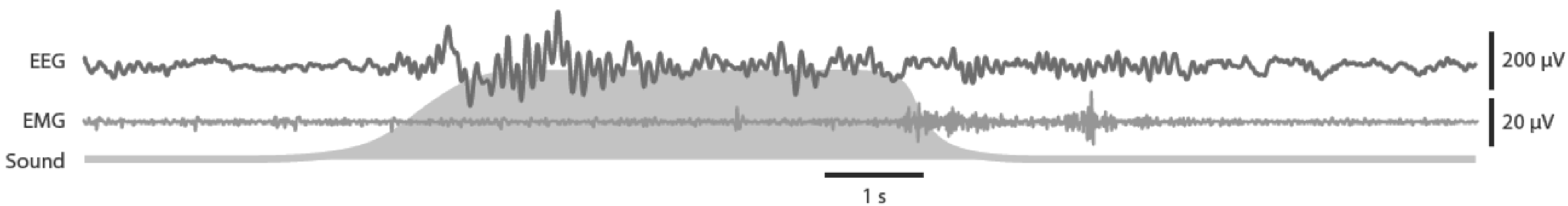
- Active Noise Control
  - "noise cancellation"
- Passive Noise Control
  - Source
    - "shhh!"
    - Public policy
  - Path
    - Ear plugs
    - Architecture and materials
- Sound Masking
  - ("white" noise)

- Human Physiology
  - What brain-based factors are involved in dampening sound perception during sleep?
  - Can they be measured to identify who is at risk of noise-induced sleep disruption, and when?
  - Can these systems be manipulated (drug, device, or behavior)?

Approaching the Problem

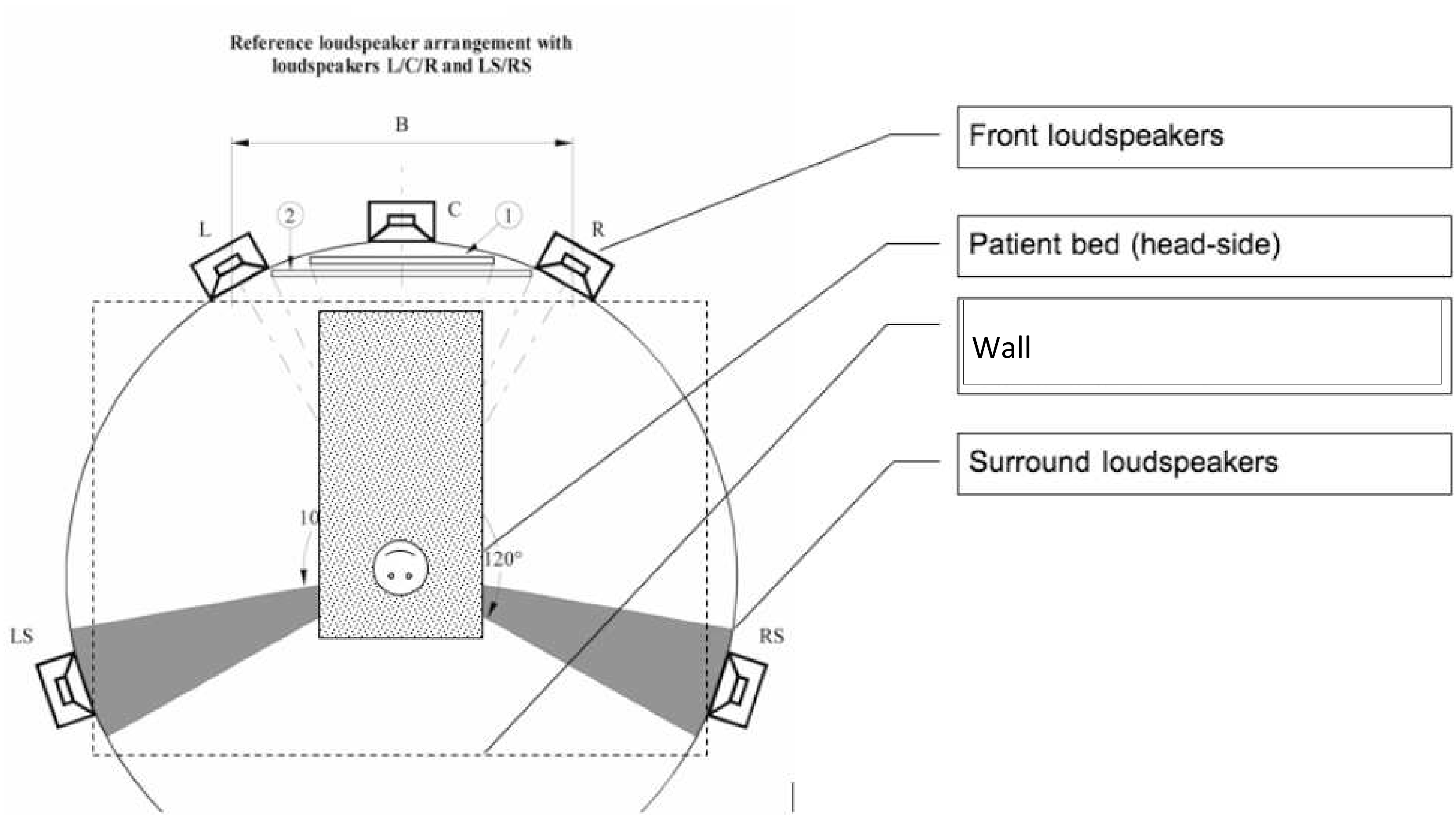
- Predictors
  - Hypotheses: noise-induced disruption of sleep will be governed by…
    - Sound level (e.g., 65 dB)
    - Sound type (e.g., traffic)
    - Sleep physiology
      - Sleep stages
      - Spindles (individual traits, between subjects)
      - Alpha oscillations (instantaneous states, within subjects)
- Subjects:
  - 13 healthy subjects (median age = 24)
- Methods:
  - 3 nights (1 quiet; 2 noisy)
  - 14 hospital sounds
- Outcome
  - Probability of disrupted sleep ("EEG arousal")

Sound-induced sleep disruption (arousal)

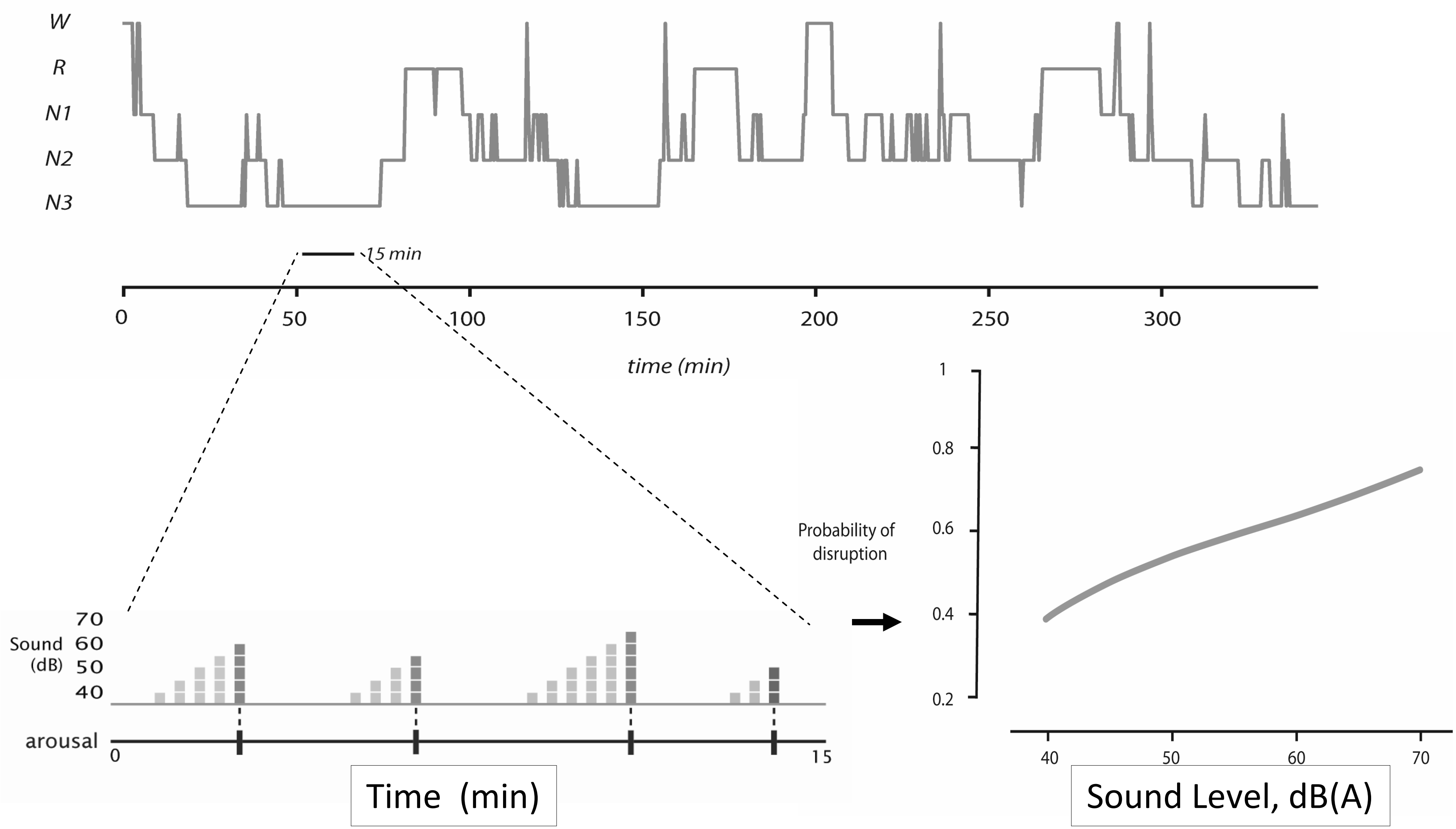


Sound in Sleep: The Set Up

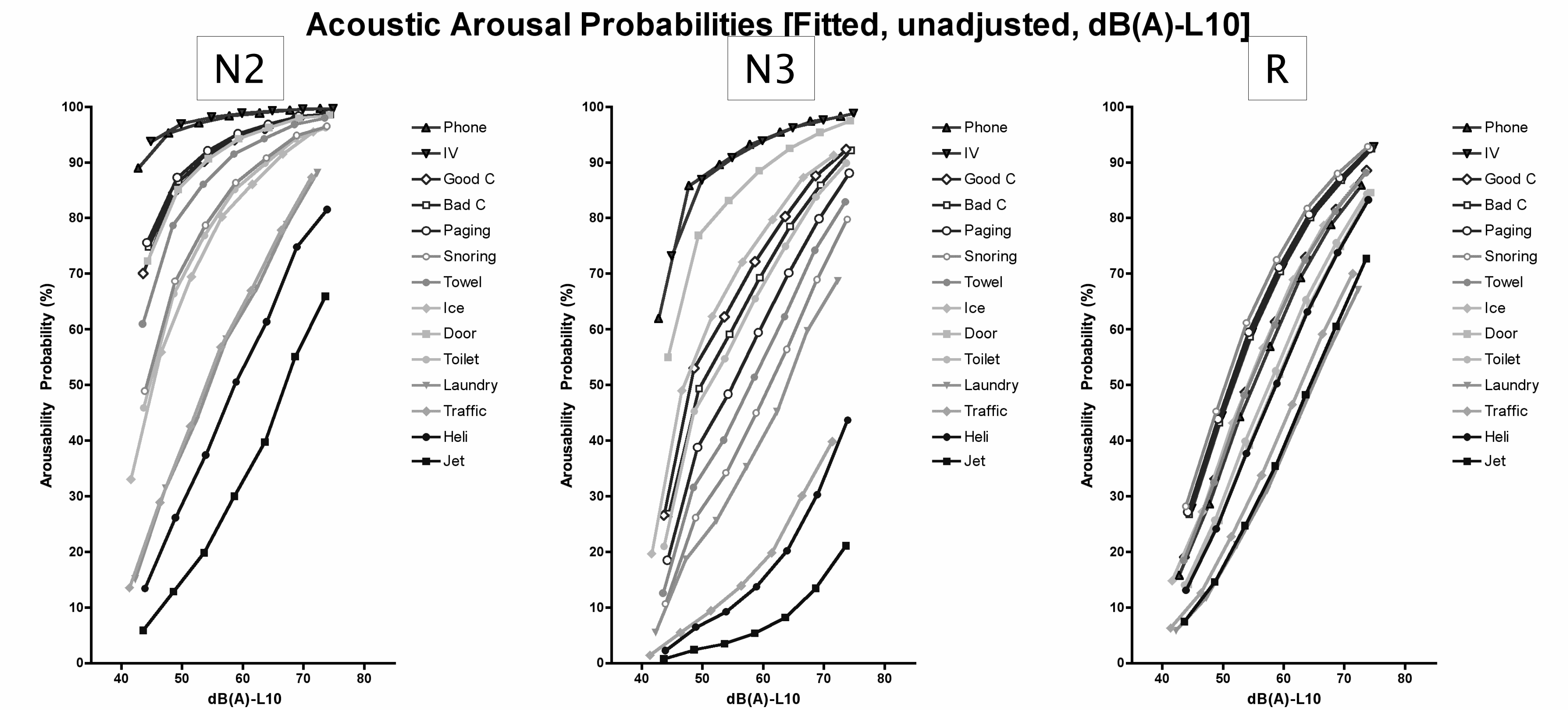
Sound in Sleep: The Set Up



Probing sleep depth

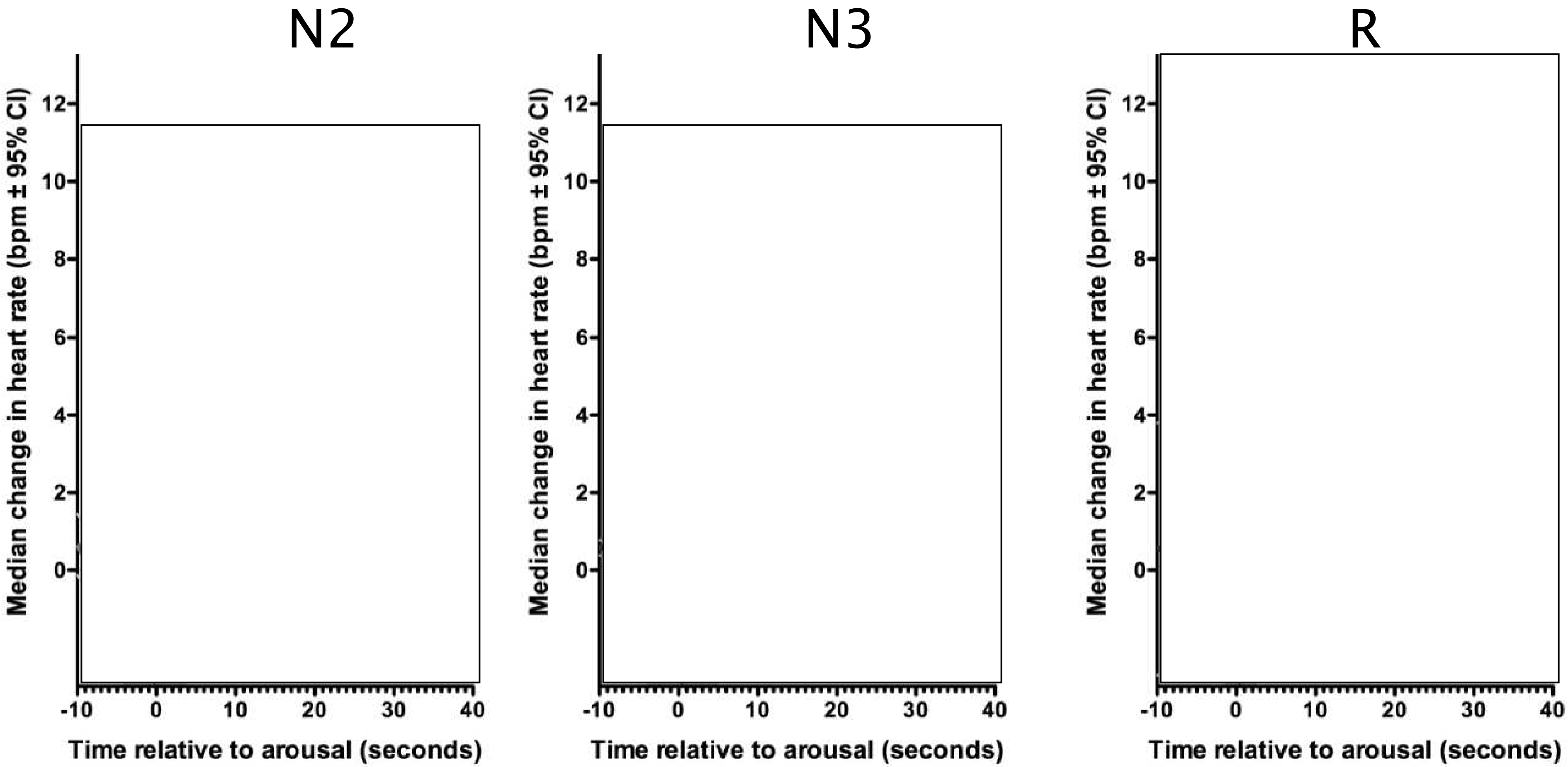


Probability of Arousal: Sleep Stages



Buxton, Ellenbogen et al, Annals of Internal Medicine, In press

Heart-Rate Response to Arousals



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Outline

Noise and Sleep

- Background

Questions to be addressed

- Biological drivers of stable sleep
    - Sleep stages
    - Traits
    - States

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- Summary/Conclusions
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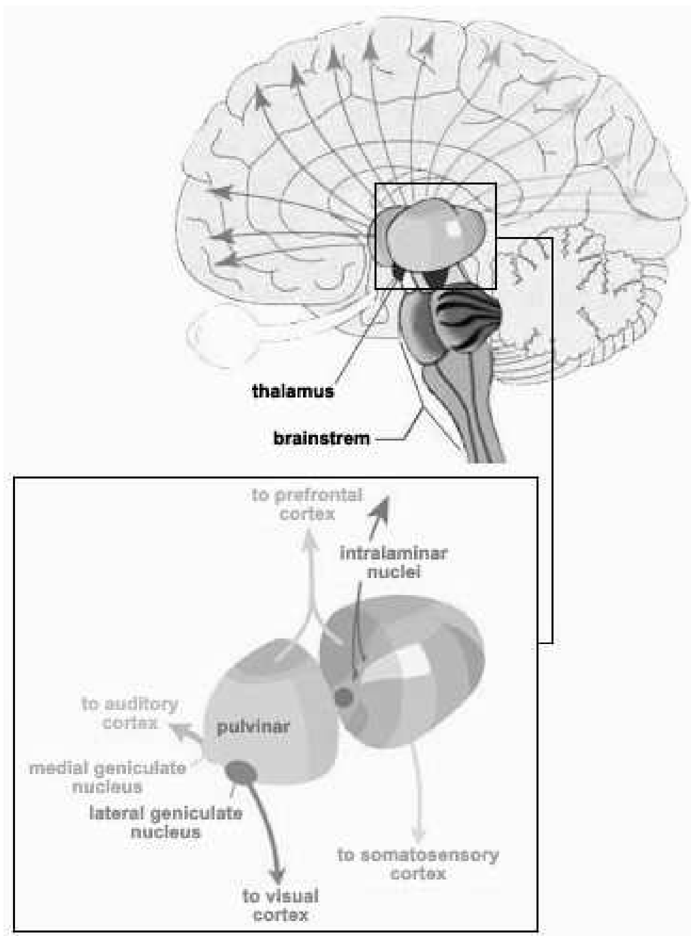
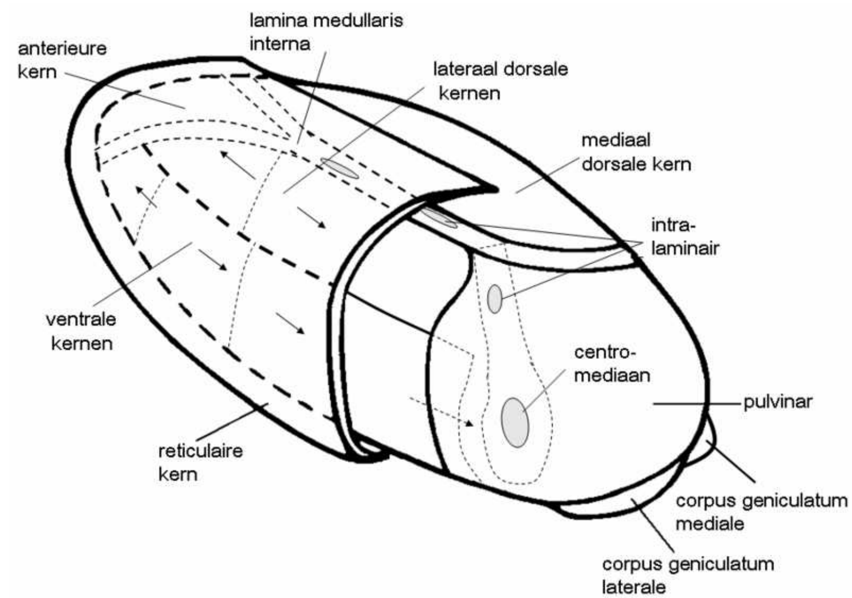
Biomarkers of stable sleep

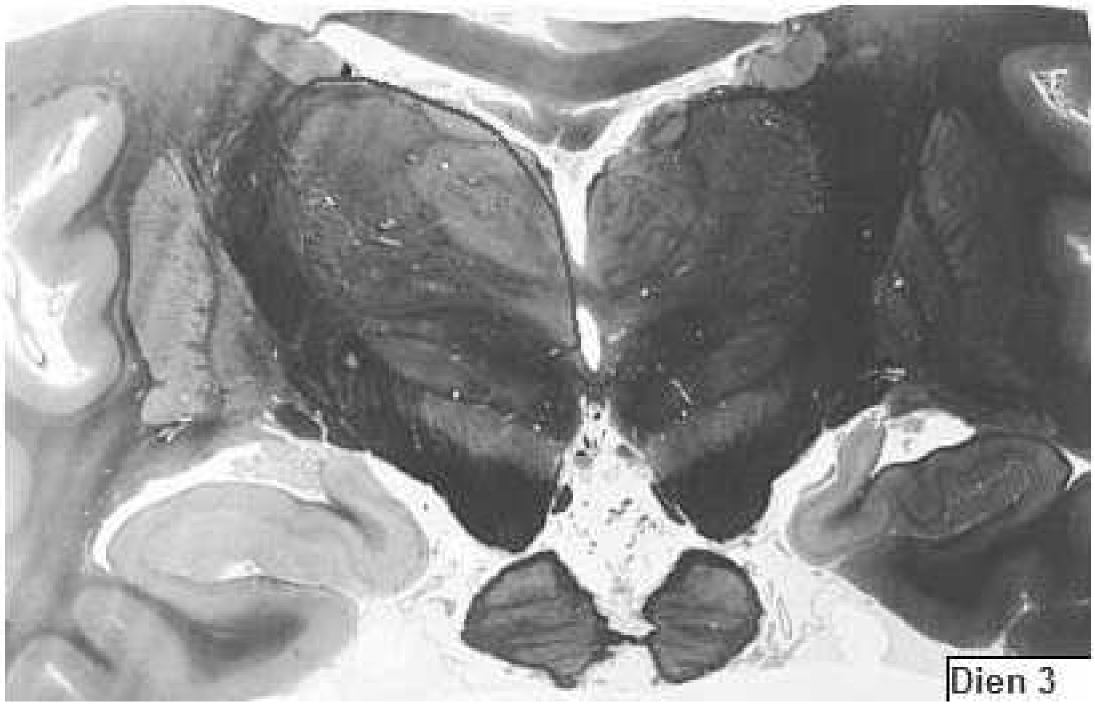
- Traits: Sleep spindles
  - Background:
    - » Thalamus is the gateway of sensory information
    - » Thalamus generates spindles
    - » Rate of spindles are stable night-to-night for a person
  - Hypotheses:
    - » thalamus reduces sensory input to the neocortex during sleep, maintaining sleep when confronted with noise
    - » The degree of this scrutiny during sleep varies by individual
    - » Spindle serves as a marker for this phenomenon

Thalamus gaits sensory input





Thalamus

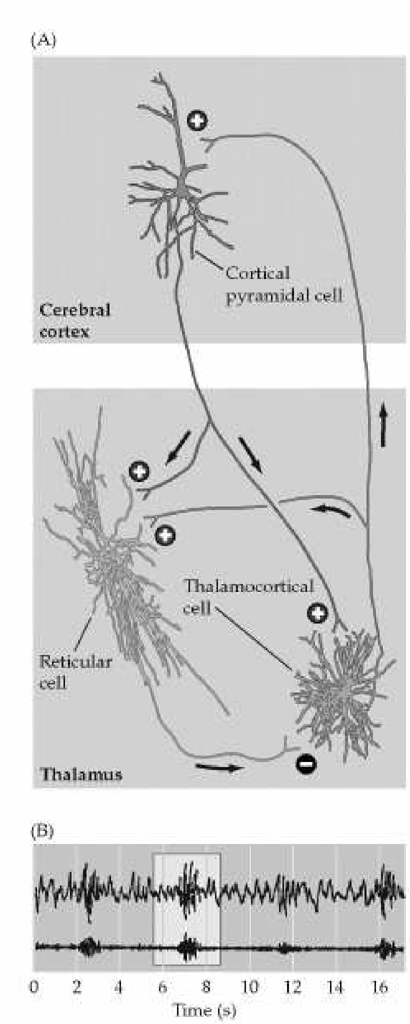


http://isc.temple.edu/neuroanatomy/lab/atlas/mdbg/

Reticular Formation

http://isc.temple.edu/neuroanatomy/lab/atlas/mdbg/

Thalamus generates spindles: mechanism

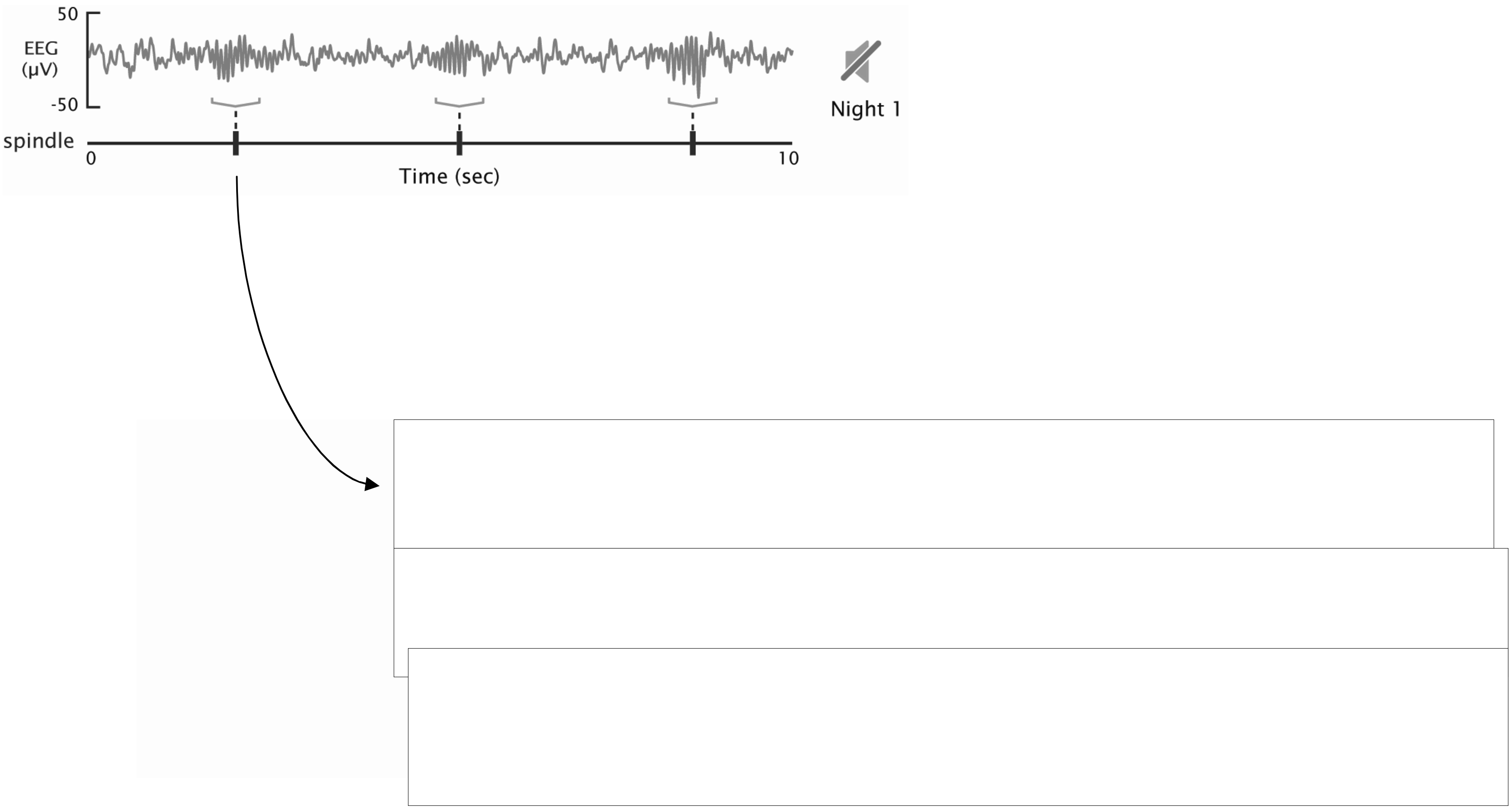


Three-neuron system:

- –Reticular neurons of the thalamus
  - •Rhythmic sequences
- –Thalamocortical neurons (TC)
- –Corticothalamic neurons
  - •Widespread synchronization

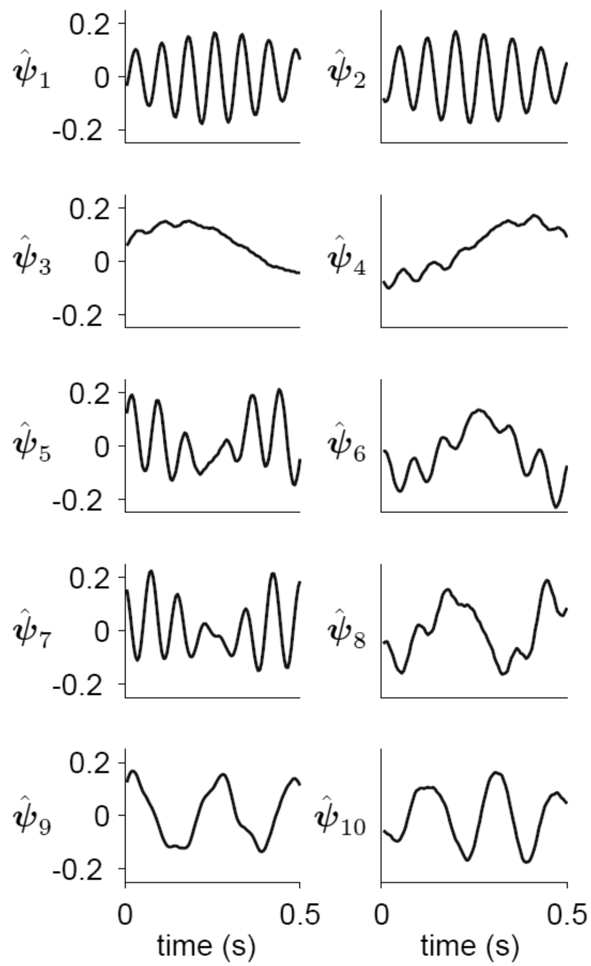
Steriade 2005

Automated spindle detection



Dang-Vu et al Current Biology 2010

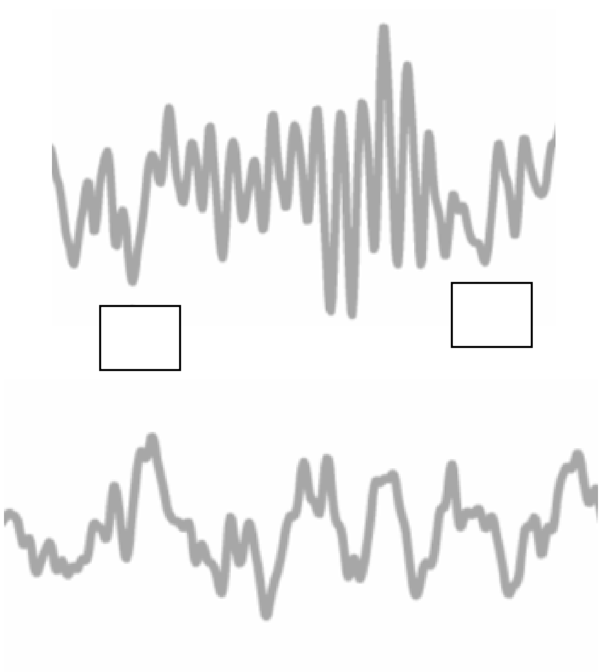
The Empirically Derived Spindle Basis



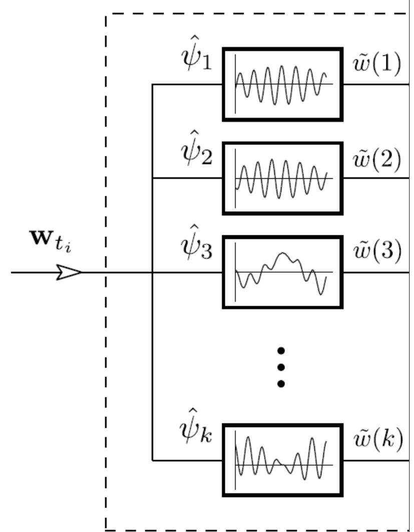
Babadi, McKinney et al. IEEE Transactions in Biomedical Engineering. 2012

Bayesian Inference for Spindle Detection:
Using parametric model of transform coefficient distributions

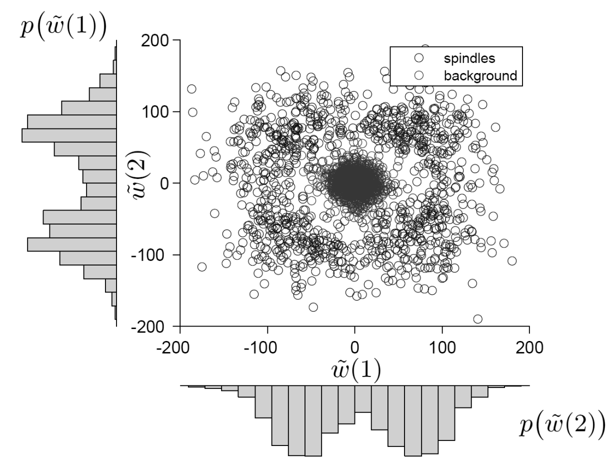
Project EEG segments…



…onto Basis



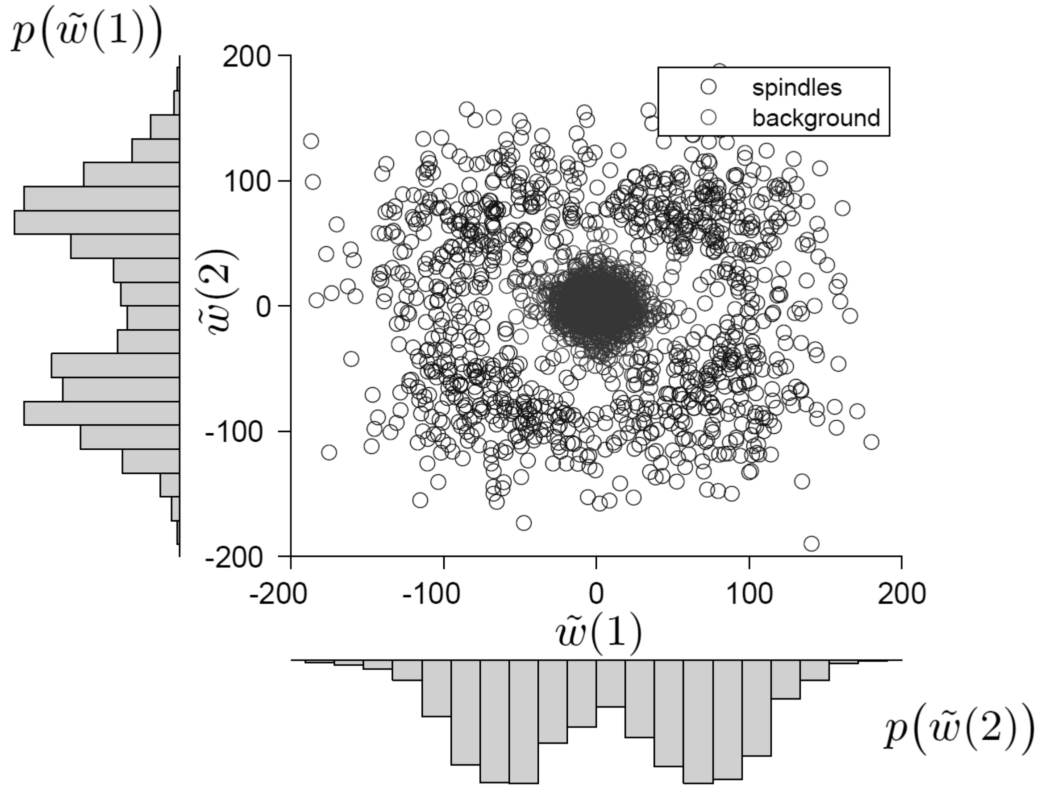
Coefficient Distributions
(using first 2 basis elements)



Babadi, McKinney et al. IEEE Transactions in Biomedical Engineering. 2012

Spindles separate from background:

Distribution of transform coefficients for 1st 2 basis elements



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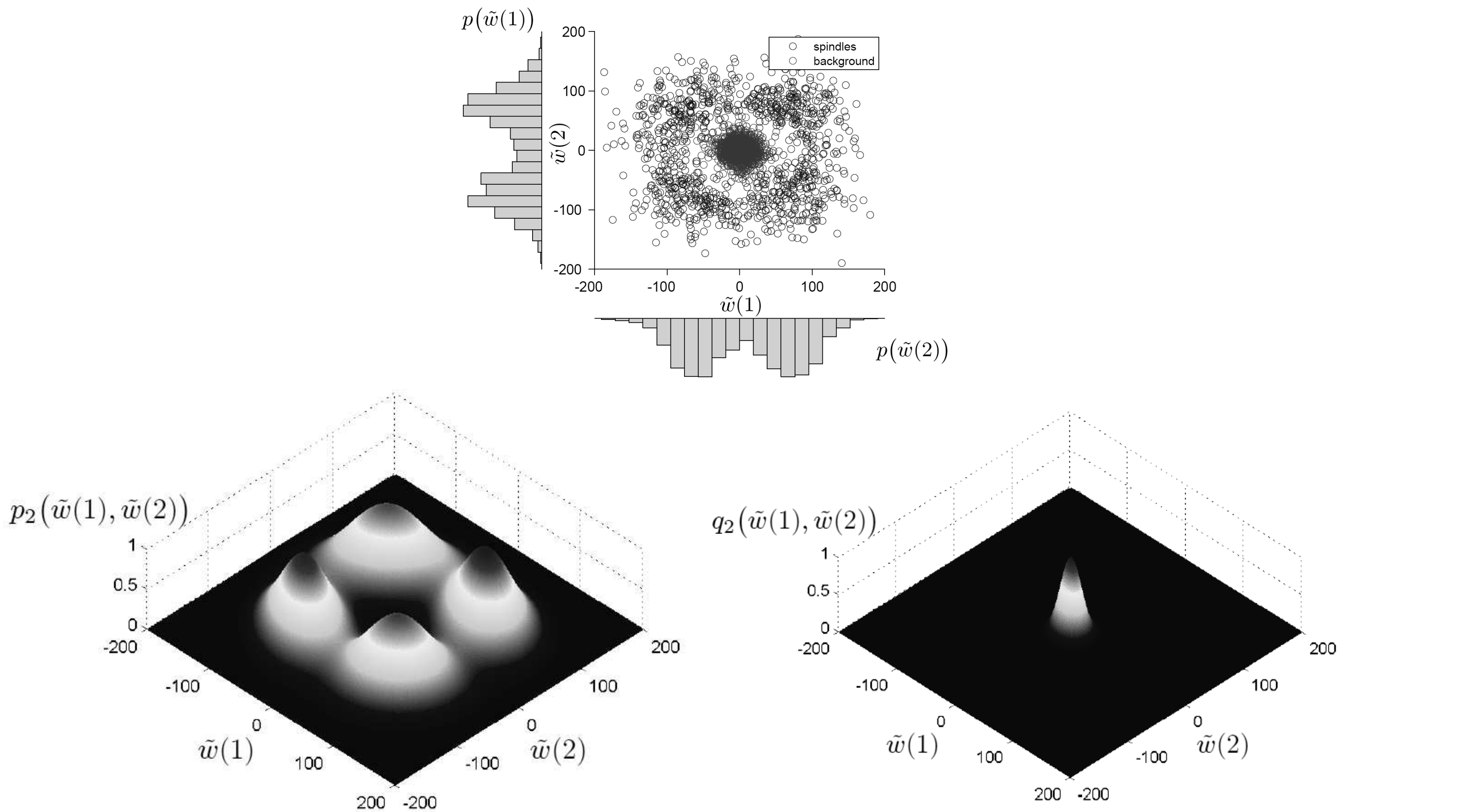

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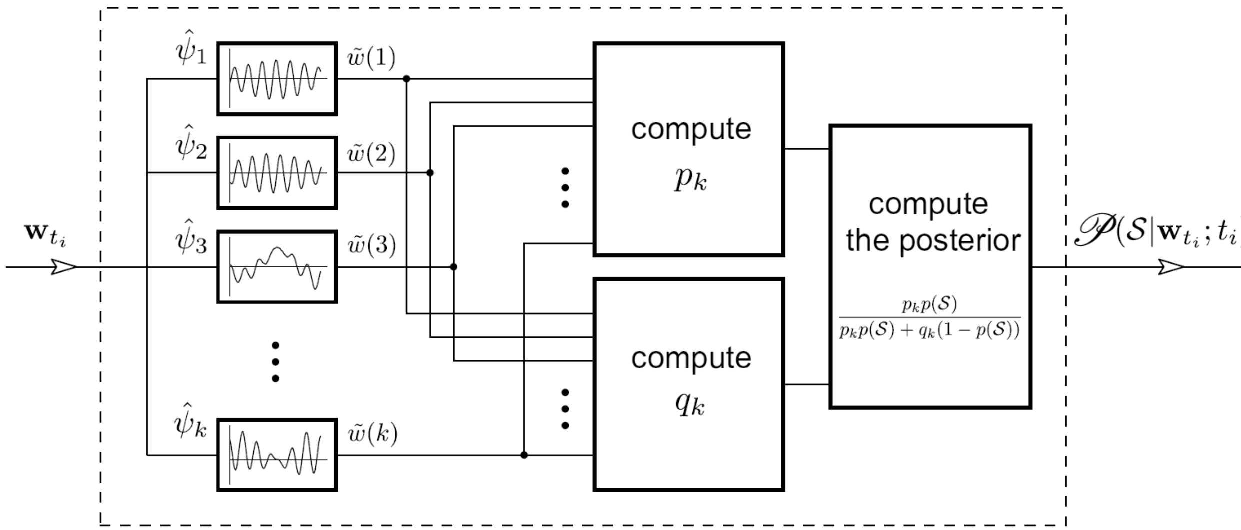
Bayesian Inference for Spindle Detection:

Using parametric model of transform coefficient distributions

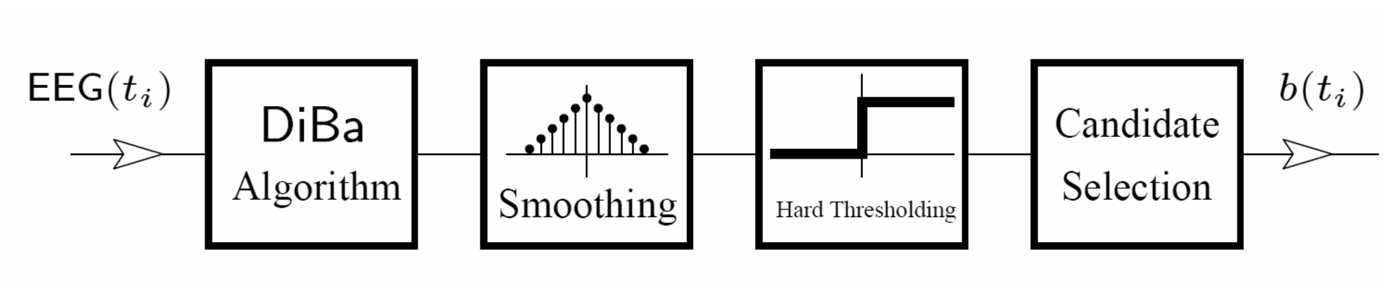
EEG
segment
(spindle?)



probability
that segment
belongs to a
sleep spindle

Babadi, McKinney et al. IEEE Transactions in Biomedical Engineering. 2012

Spindle Detection with DiBa



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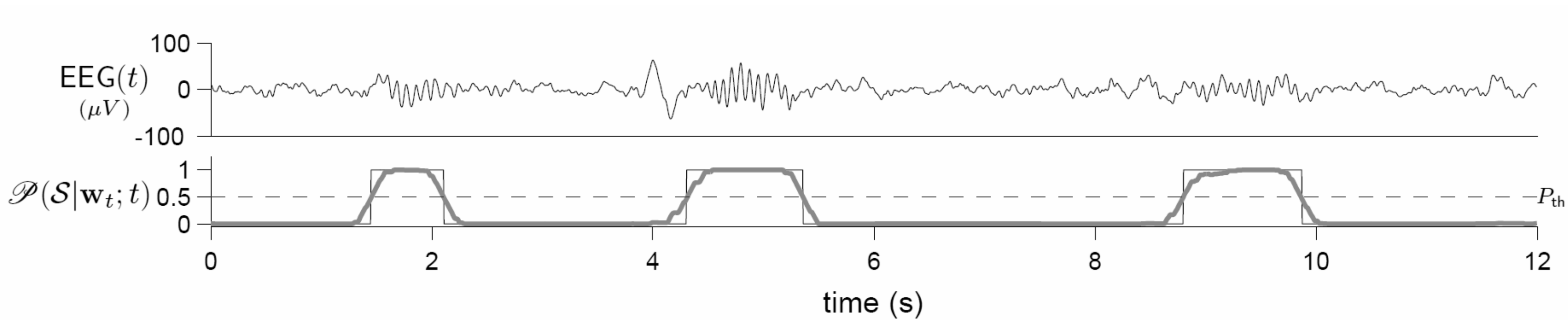
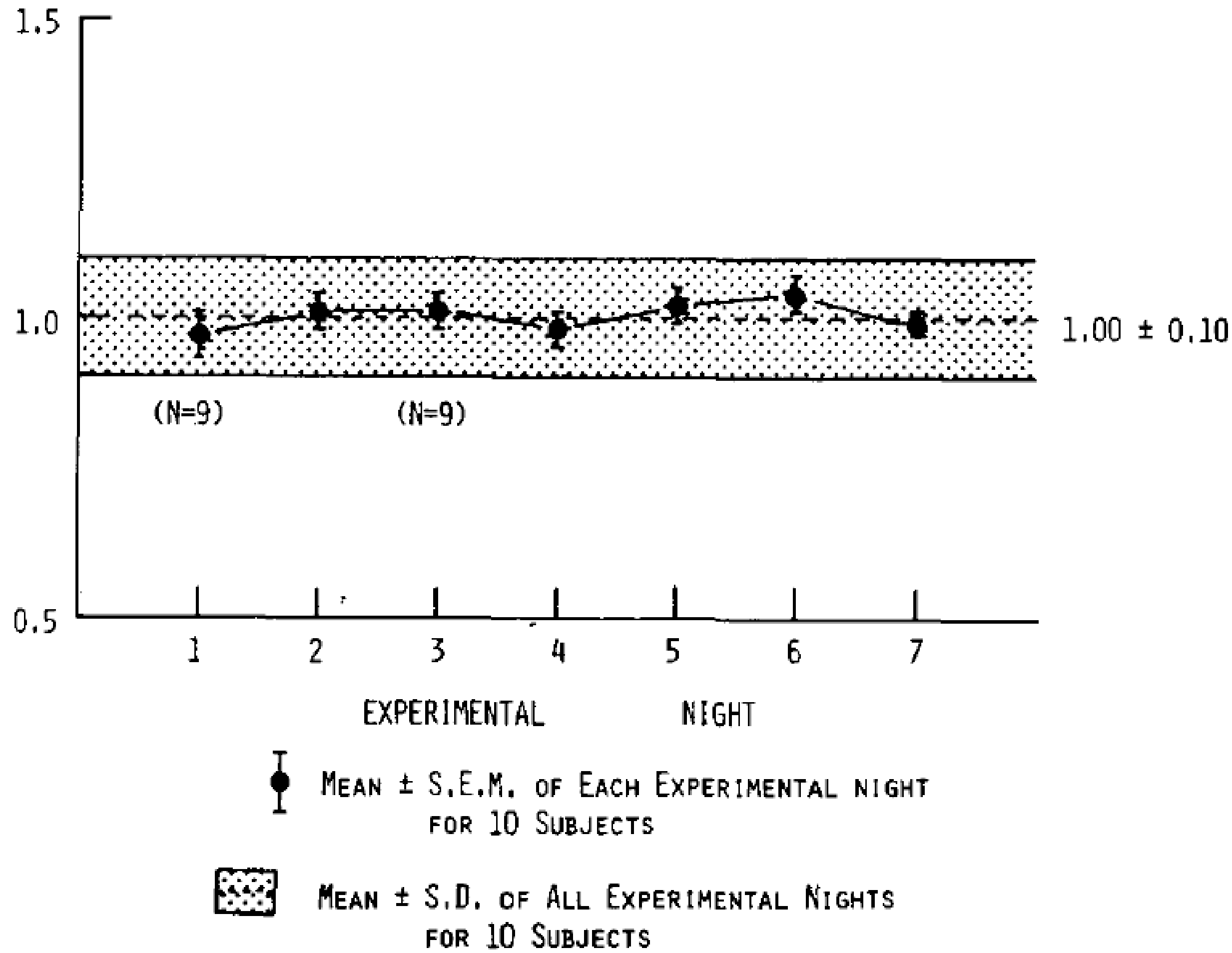
Spindle Detection with DiBa



Babadi, McKinney et al. IEEE Transactions in Biomedical Engineering. 2012

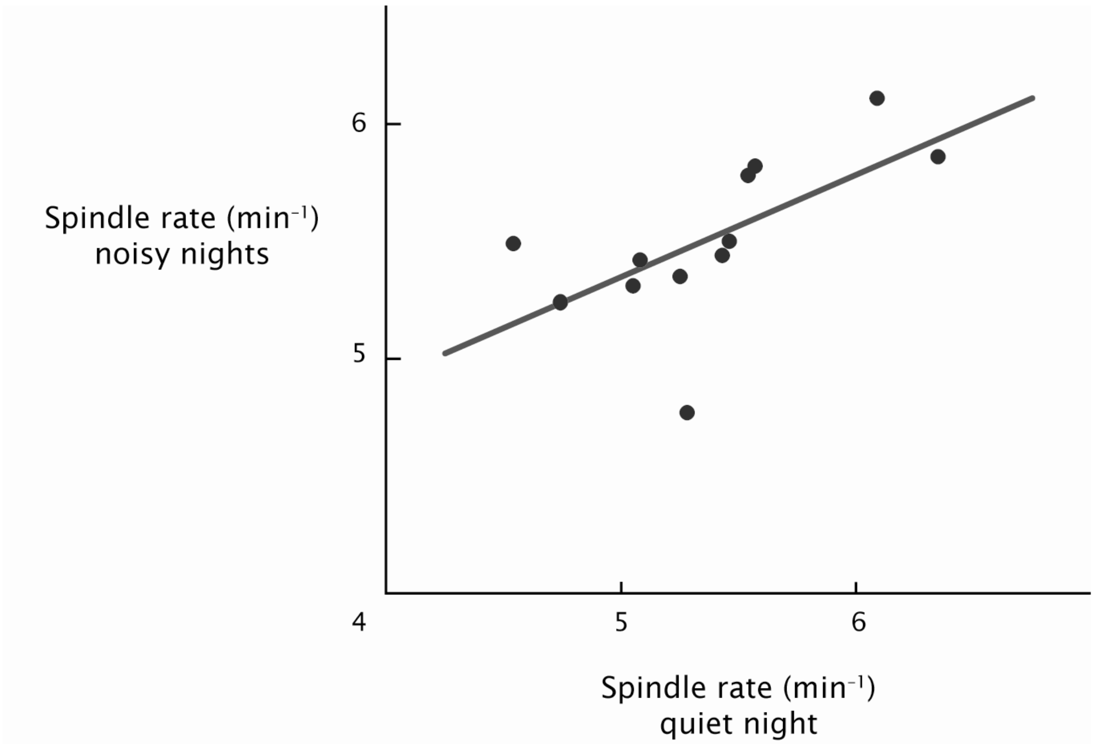
Spindle rate is consistent across nights

spindle rate/
mean spindle rate



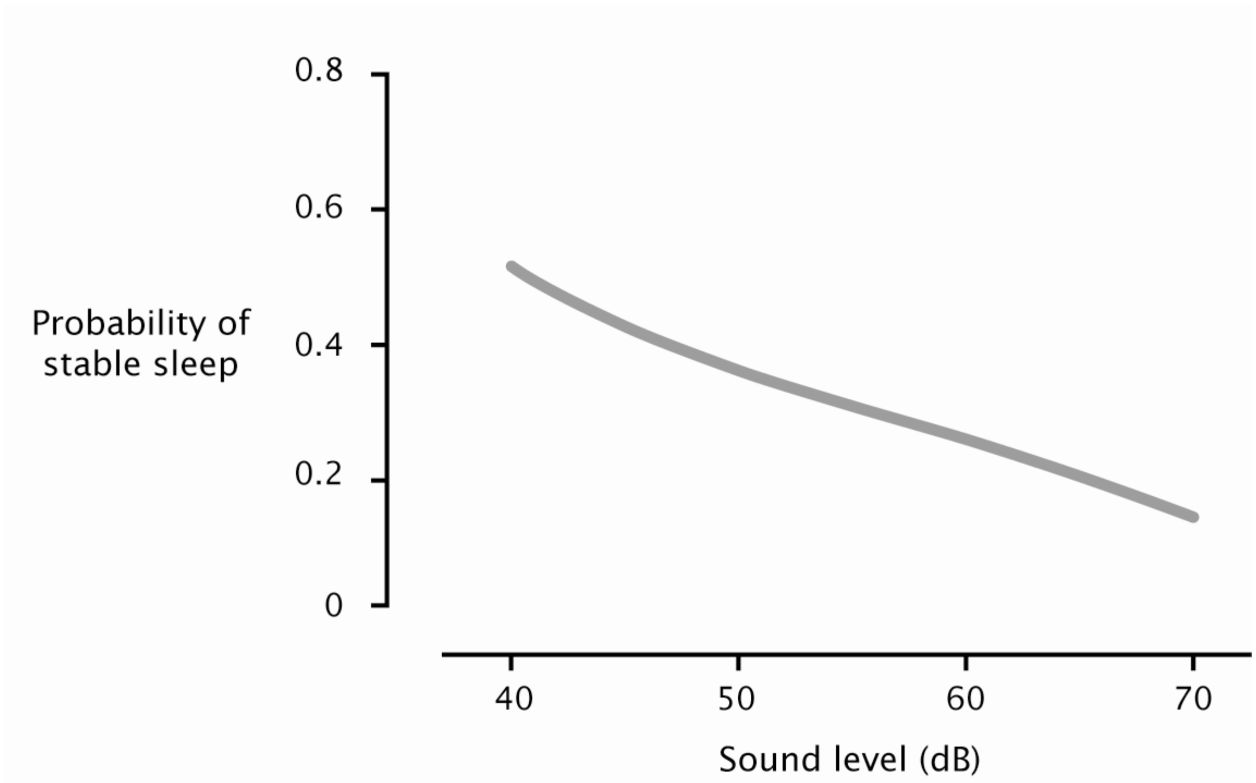
Azumi, 1982

Spindle rate is consistent across nights



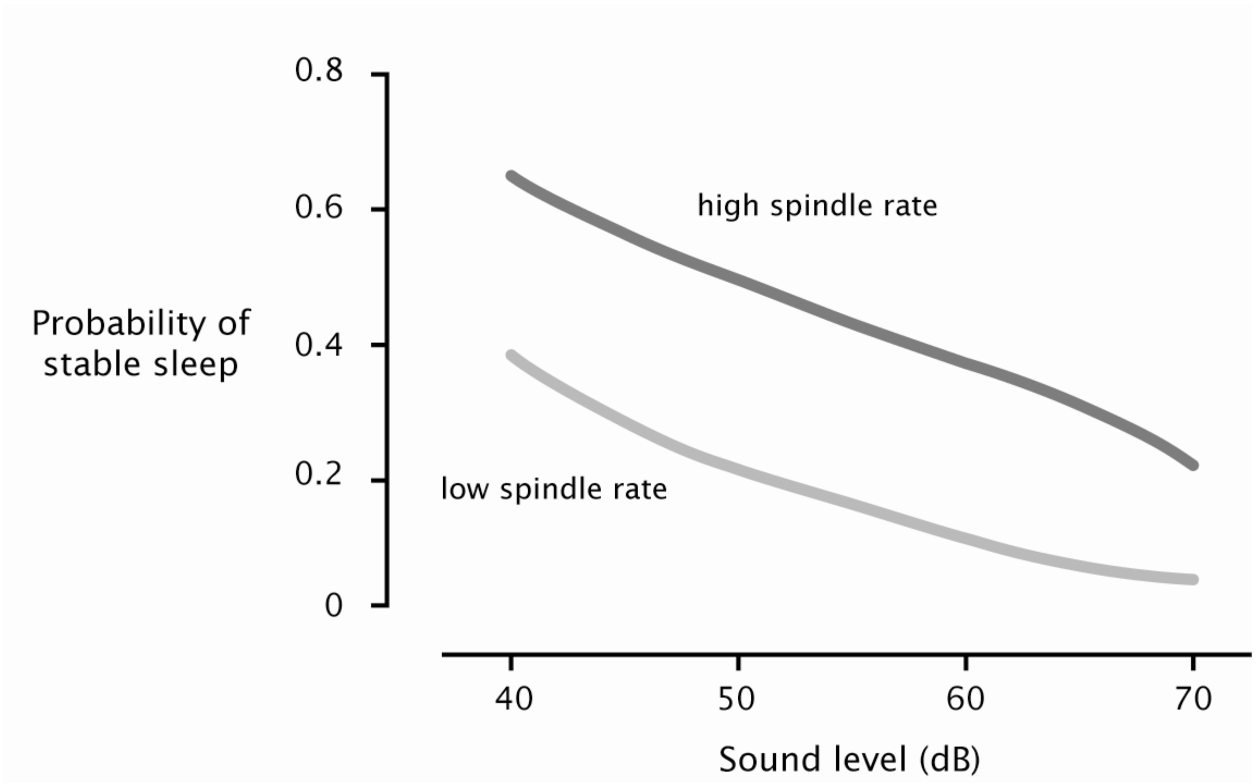
Dang-Vu et al Current Biology 2010

The sleep survival curve



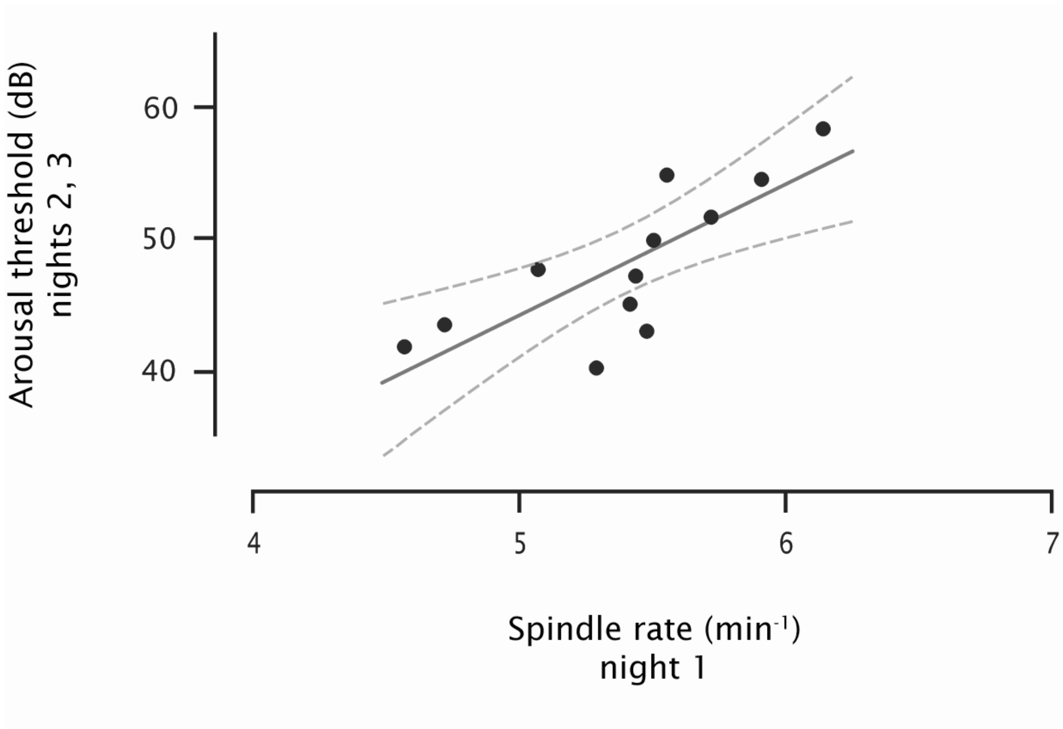
Dang-Vu et al Current Biology 2010

Sleep stability by spindle rate



Dang-Vu et al Current Biology 2010

Spindle rate predicts mean arousal threshold



Dang-Vu et al Current Biology 2010

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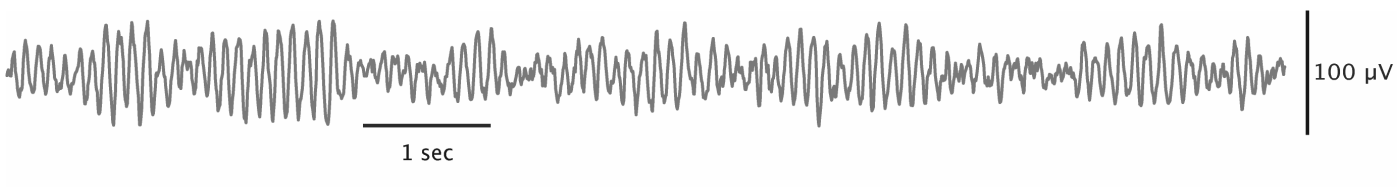
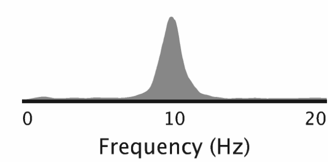
Biomarkers of stable sleep

- States: Alpha power
  - Background:
    - » Hallmark waking rhythm (vigilance)
    - » Fluctuates in sleep
  - Hypothesis:
    - » oscillatory features of the EEG (alpha activity, 8-13 Hz) predict disruption of sleep from noises
    - » …and can do so in real time

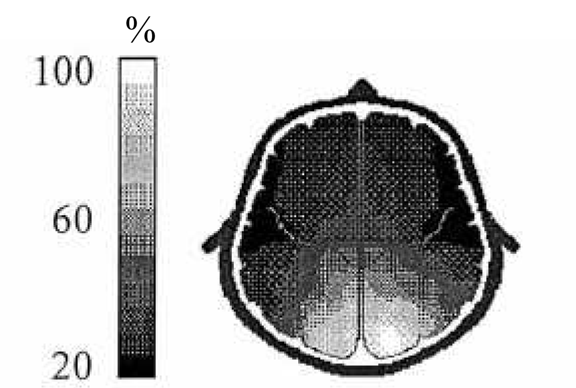
The alpha rhythm





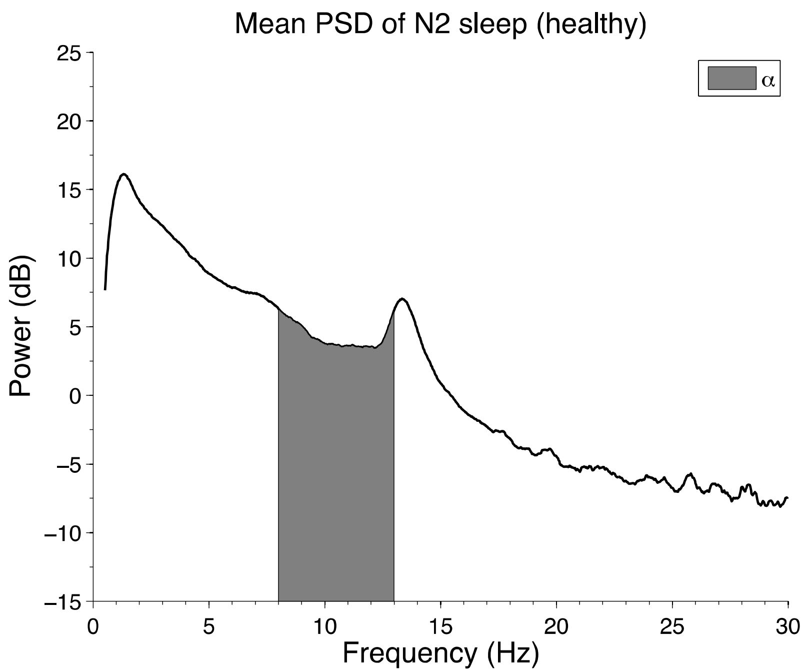
Raw signal, time domain, derived from occipital electrode

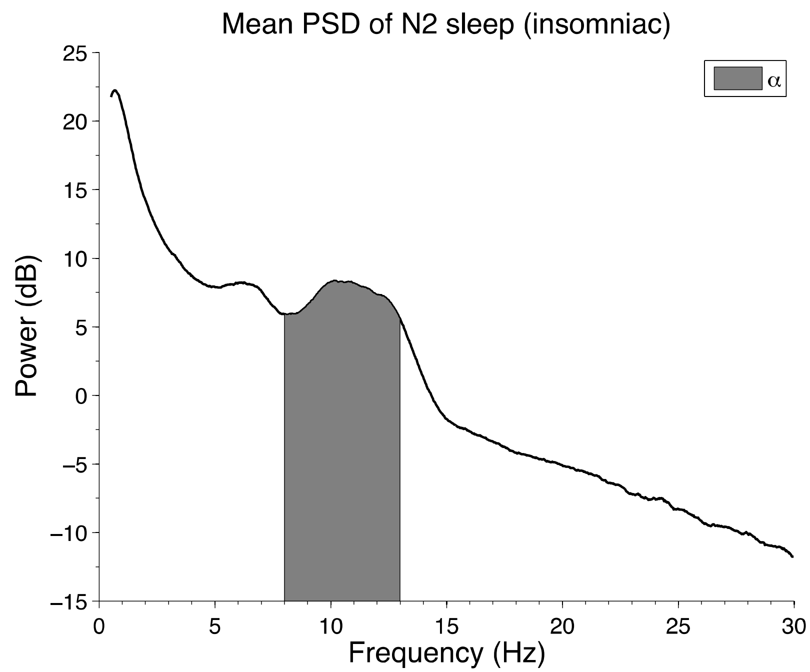
Frequency domain



Cantero, 2002

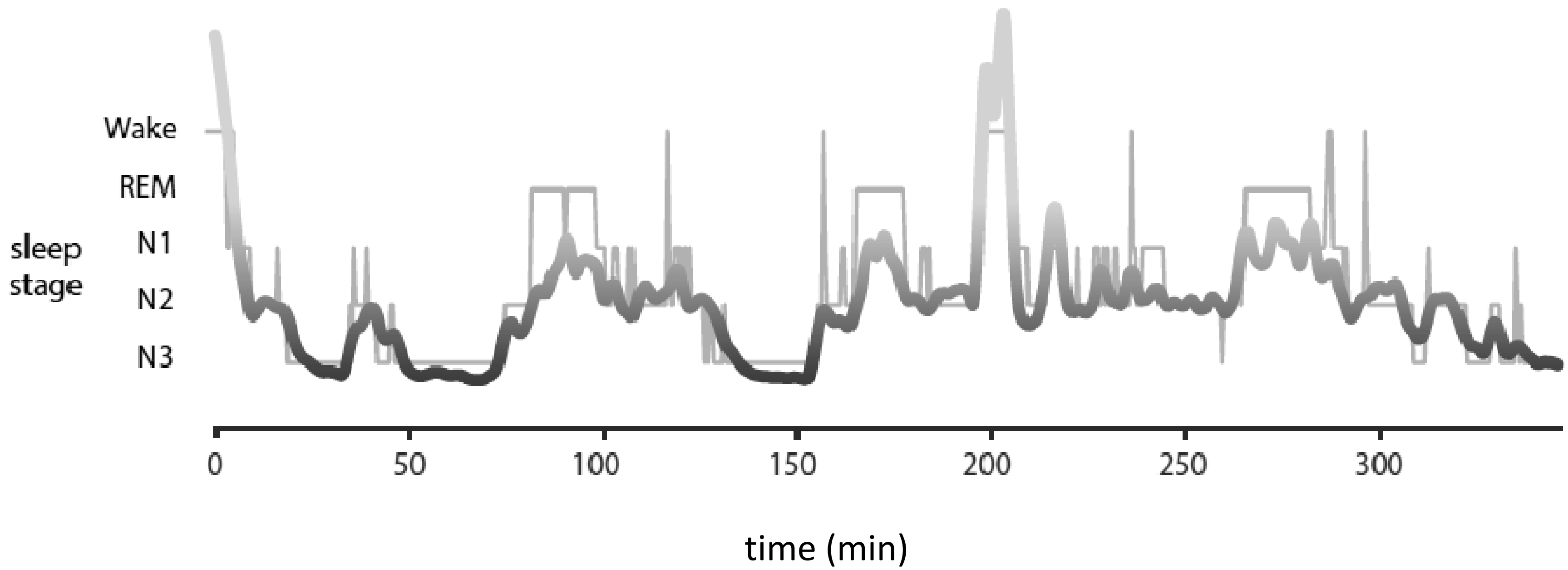
Insomnia: Light sleeper = heavy alpha?





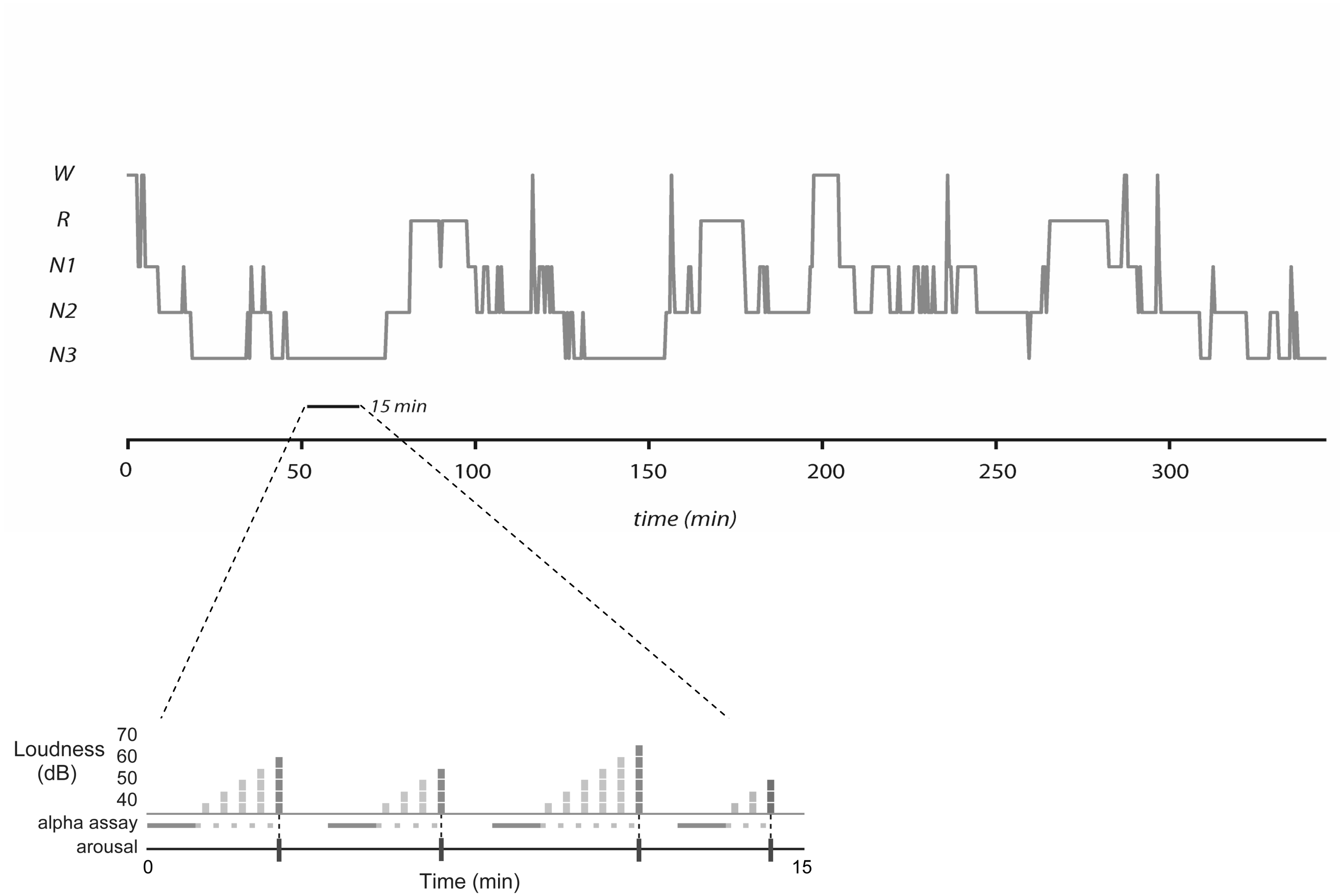
(new, unpublished data)

Alpha power fluctuates, even within a sleep stage

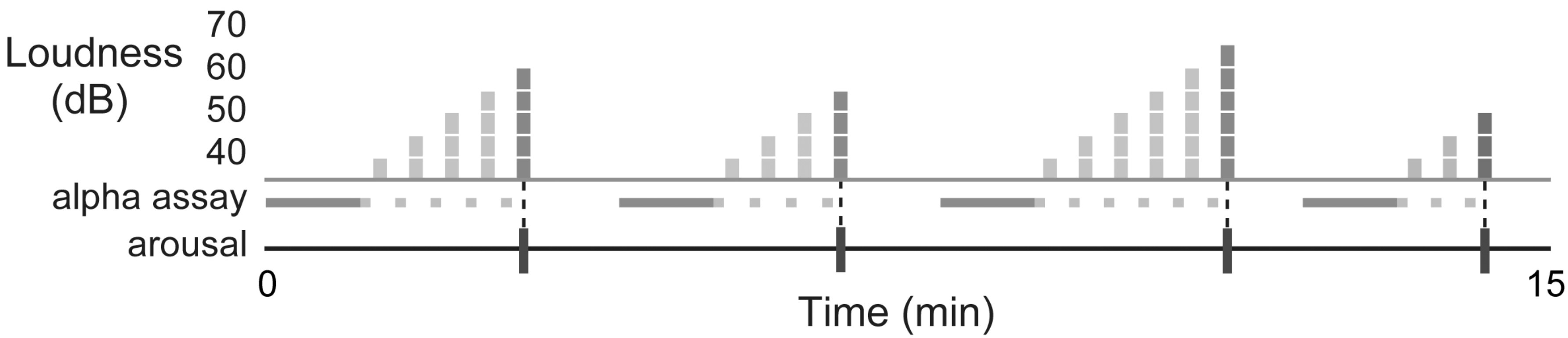


McKinney et al. PLoS One. 2011

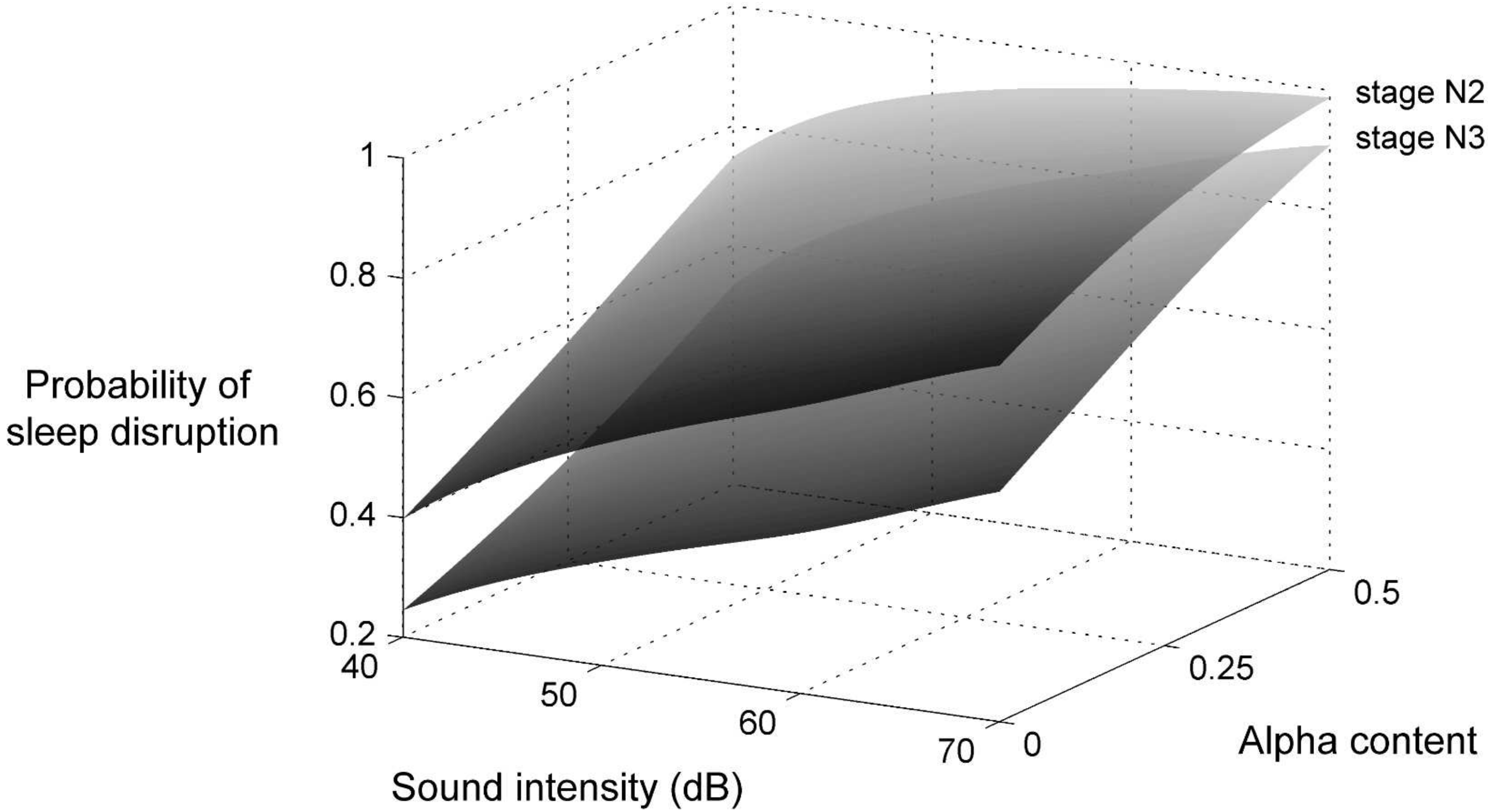
Probing sleep depth



Probing sleep depth: Pre-stimulus EEG



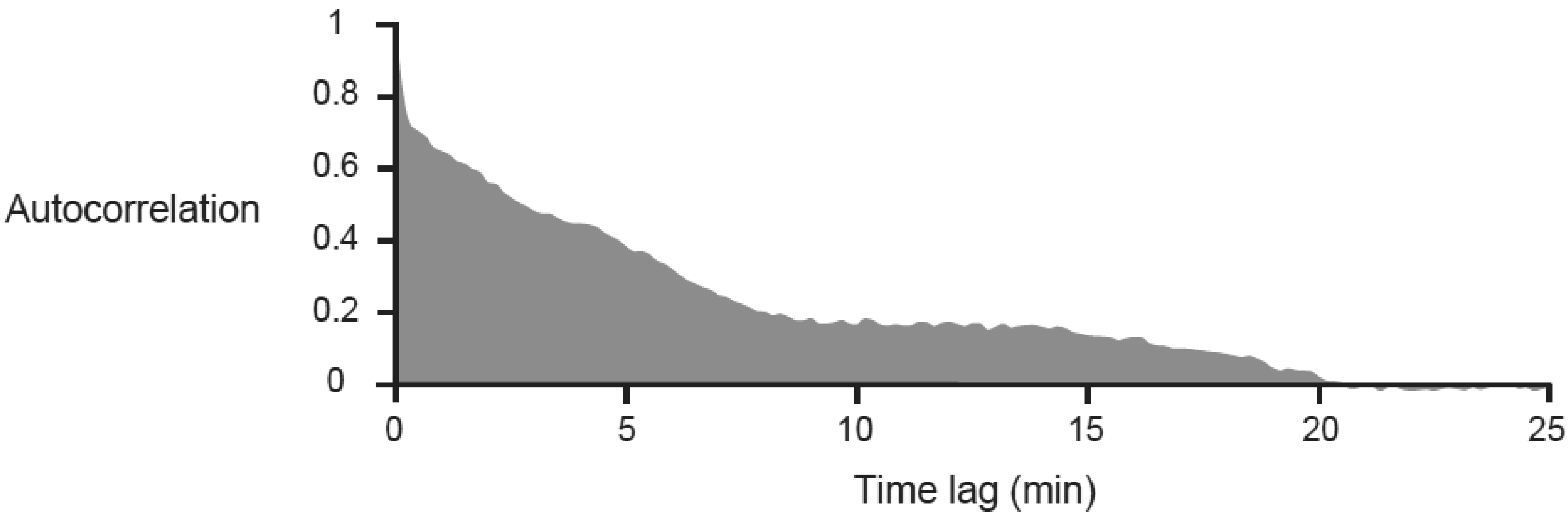
Alpha power modulates sleep fragility



*Not significant in REM

McKinney et al. PLoS One. 2011

How Stable Is Alpha Activity During Sleep?



McKinney et al. PLoS One. 2011

Theories of Alpha

- Possible interpretations
  - Idling (i.e., more alpha means more inactive)
  - Vigilance (i.e., more alpha means more awake)
  - Inhibition (i.e., more alpha means less engaged)

Task-Irrelevant Inhibition

- BACKGROUND
  - Two-streams hypothesis
    - Ventral (what)
    - Dorsal (where)
- METHOD
  - Working-memory task
    - ID=identity of faces (what)
    - OR= orientation of faces (where)
  - MEG
  - time-frequency representations of power
- RESULTS
  - ↑α dorsal stream (parieto-occipital)
    - During ventral demanding task
    - But not dorsal demanding task
- CONCLUSION
  - α activity represents functional inhibition of task-irrelevant areas

Alpha activity over dorsal stream:

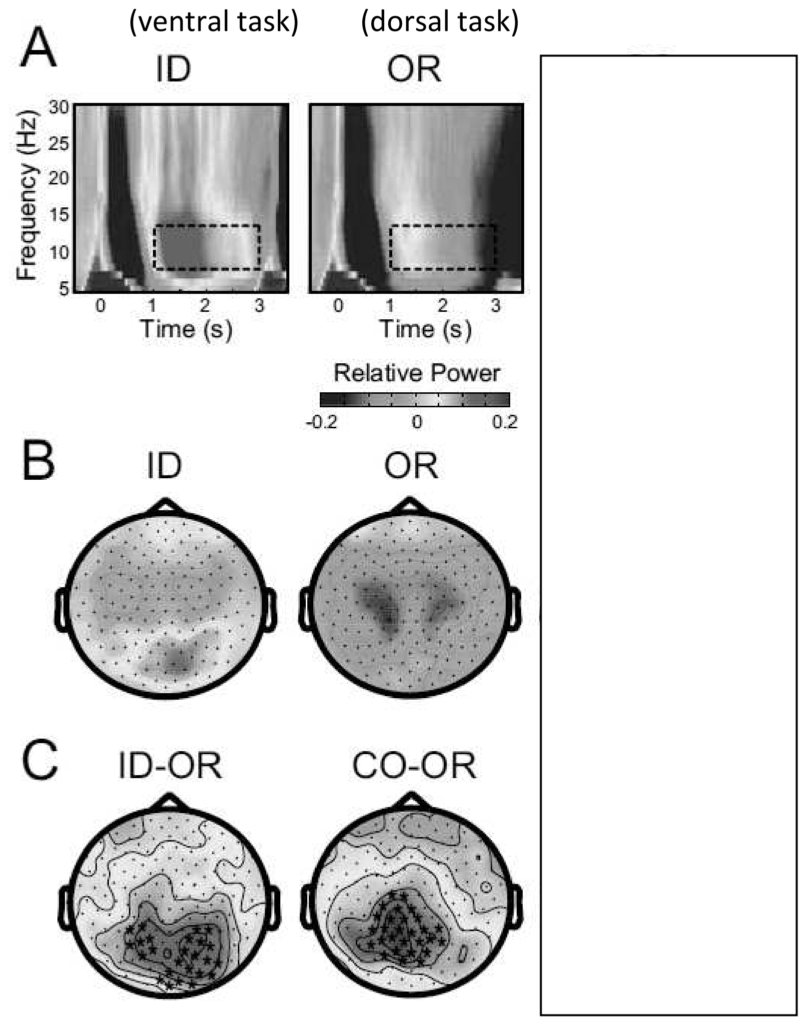


Figure 3. The alpha band activity during retention. *A*, Grand average of the TFRs of the

Jokisch and Jensen, J Neurosci 2007

Summary

- Predicting sleep disruption through…
  - 3 main determinants:
    - Louder sounds and shallower sleep predict their sleep-disruptive effects
    - Sounds cluster; less so in REM
  - TRAIT: Sleep spindles
    - Fixed properties of an individual's sleeping EEG
    - More spindles predicts more stable sleep (thalamic gaiting?)
  - STATE: Alpha activity
    - Local, moment-to-moment, transient EEG characteristics
    - More alpha predicts more vulnerable (unstable) moments of sleep
- Implications for tracking and controlling sleep: offline or online measurements of depth

Future Directions, Traits

- Modality specific finding?
  - Light, vibration, temperature, etc
  - Olfaction

- Source Localization and spatial resolution of spindles

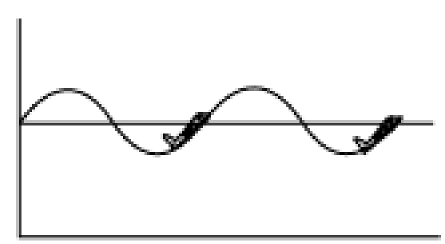
- Potential biomarker for an individual's susceptibility to noise
  - Beyond days?
  - Stable across lifecycle?

- Potential therapeutic target (can they be modified?)
  - Some sedating drugs adjust spindles
  - Some diseases alter spindles (e.g., schizophrenia)

- Relationship of spindles to cognition
  - Sleep protective, or more?

Future Directions, States

- Modality specific finding?
  - Light, vibration, temperature, etc
  - Olfaction
- α in wake vs. α sleep, a similar mechanism?
  - Does α in sleep represent task-irrelevant inhibition?
    - high-density EEG to compare this effect in occipital cortex compared to auditory cortex
    - Examine other frequency bands (gamma, etc), looking for inverse correlations between gamma and alpha (pulsed inhibition?)
  - MEG and fMRI
- Therapies to enhance sleep stability (dynamic stability)
  - Drug
  - Brain-computer interface



Acknowledgements

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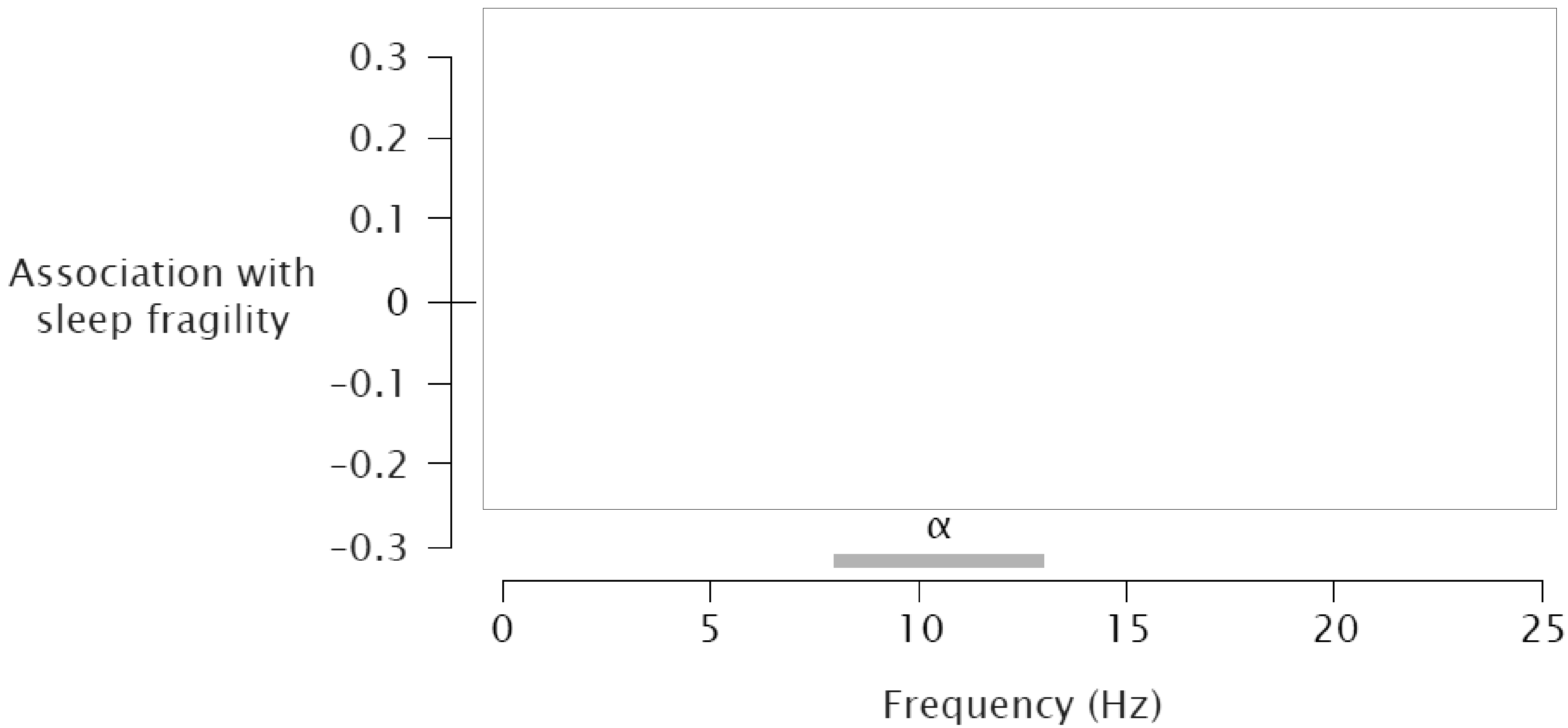
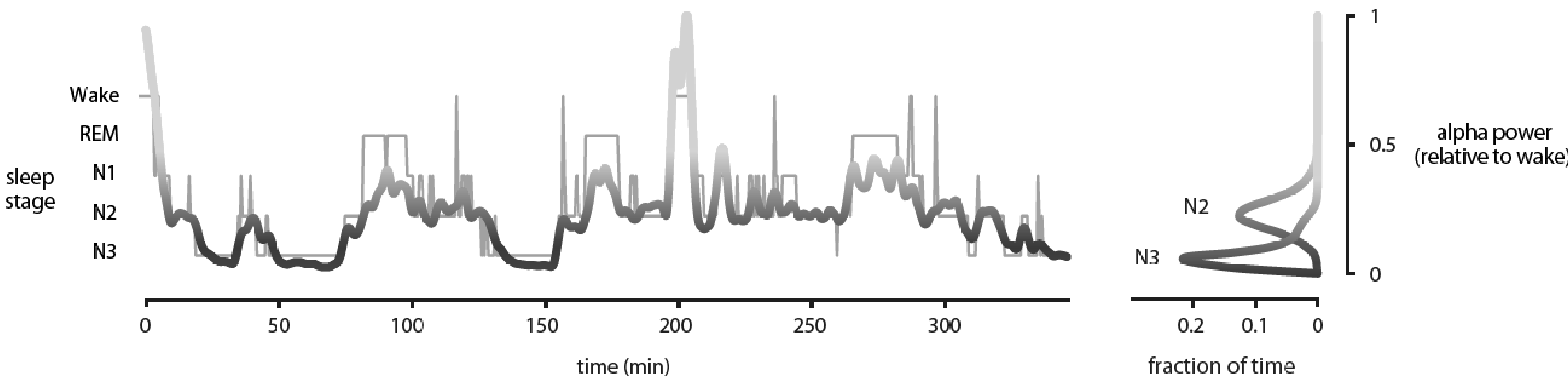
Dan Cooper

Vahid Tarokh
Behtash Babadi

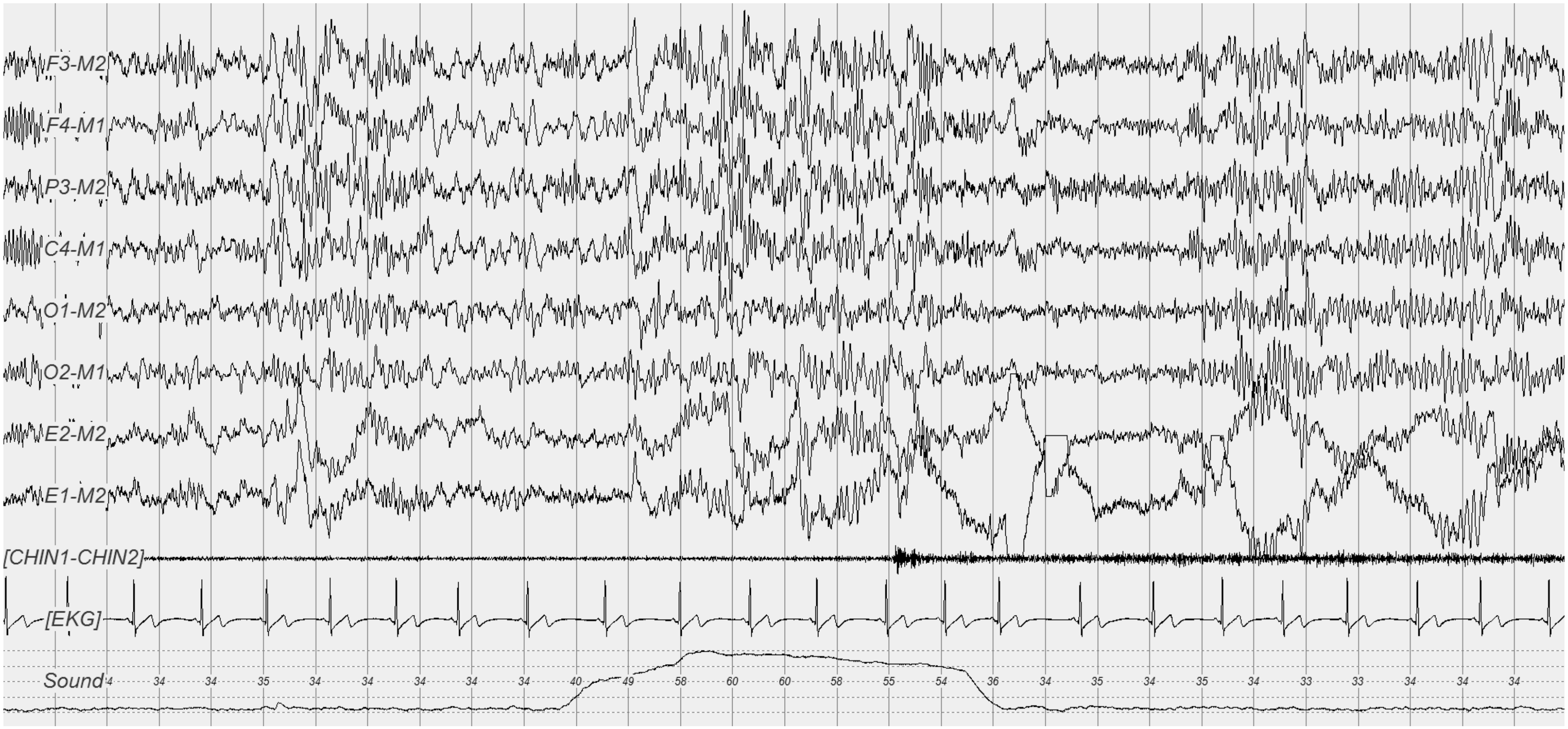
Sleep Fragility Across More Frequencies



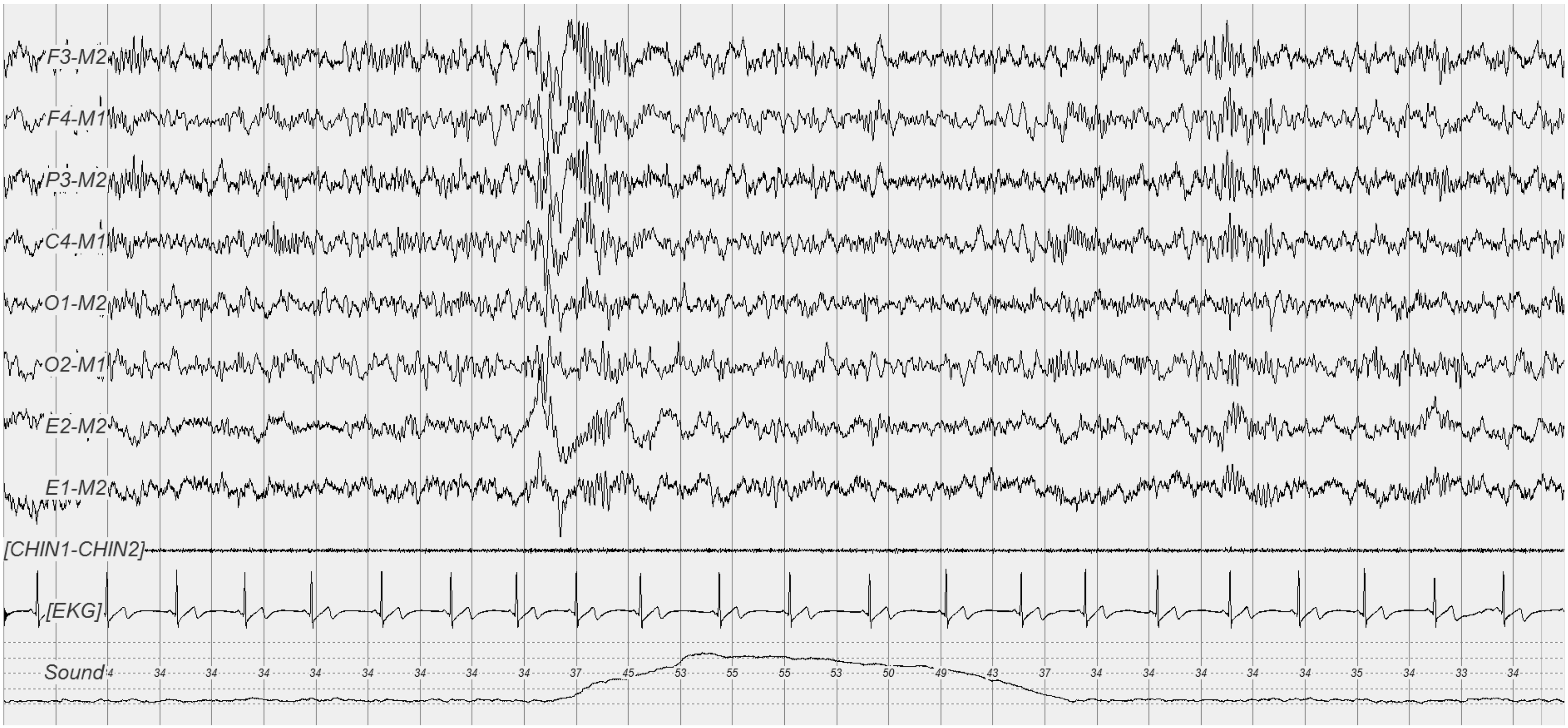
Bimodal Alpha



Arousal


F3-M2
F4-M1
P3-M2
C4-M1
O1-M2
O2-M1
E2-M2
E1-M2
[CHIN1-CHIN2]
[EKG]
Sound
34 34 35 34 34 34 34 34 40 49 58 60 60 58 55 54 36 34 35 34 35 34 33 33 34 34 34

No Arousal



F3-M2
F4-M1
P3-M2
C4-M1
O1-M2
O2-M1
E2-M2
E1-M2
[CHIN1-CHIN2]
[EKG]
Sound
34 34 34 34 34 34 34 34 37 45 53 55 55 53 50 49 43 37 34 34 34 34 34 35 34 33 34

Multimodal aspects of sensory input

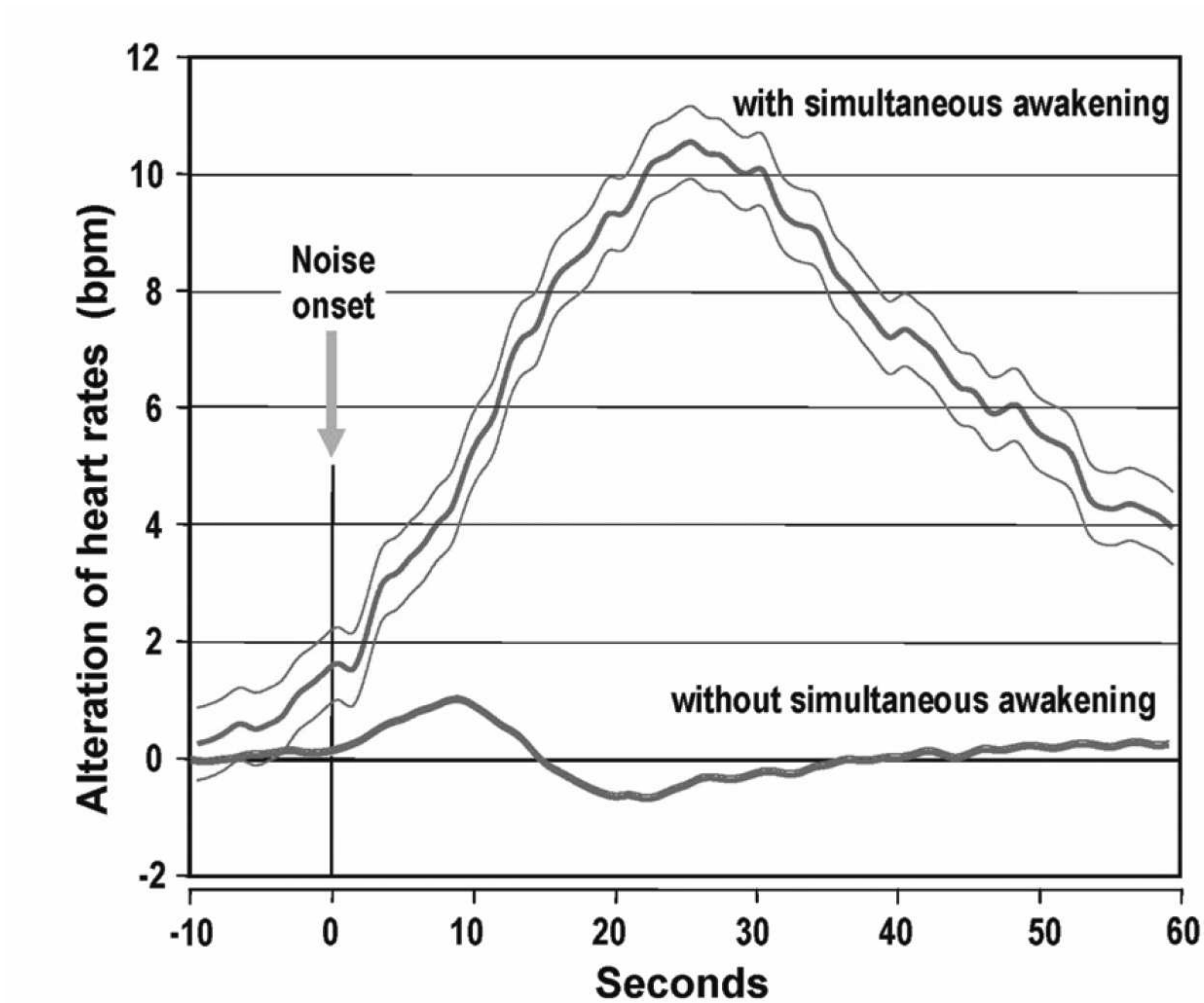
- Visual perception (seeing)
  - Visual cortex activation

- Visual imagery (imagining seeing—mind's eye)
  - Visual cortex activation
  - Auditory cortex deactivation

Amedi 2005

Experiment

- Background:
  - Sensory processing is dampened in sleep
  - Thalamus gaits sensory information to the brain
  - Spindles are an EEG marker of thalamic activity during sleep
- Hypothesis:
  - <u>Do sleep spindles signal a dampening of noise perception</u> by the thalamus during sleep?
  - If so, <u>does the amount of spindles predict sound tolerance in sleep?</u>
- Subjects:
  - 13 healthy subjects (median age = 24)
- Method:
  - Normal sleep (1 night): spindle counting
  - Acoustically disrupted sleep (2 nights). 14 sounds
- Predictor: sleep spindles on a baseline night (central electrodes)
- Outcome measure: probability of arousal on a noisy night

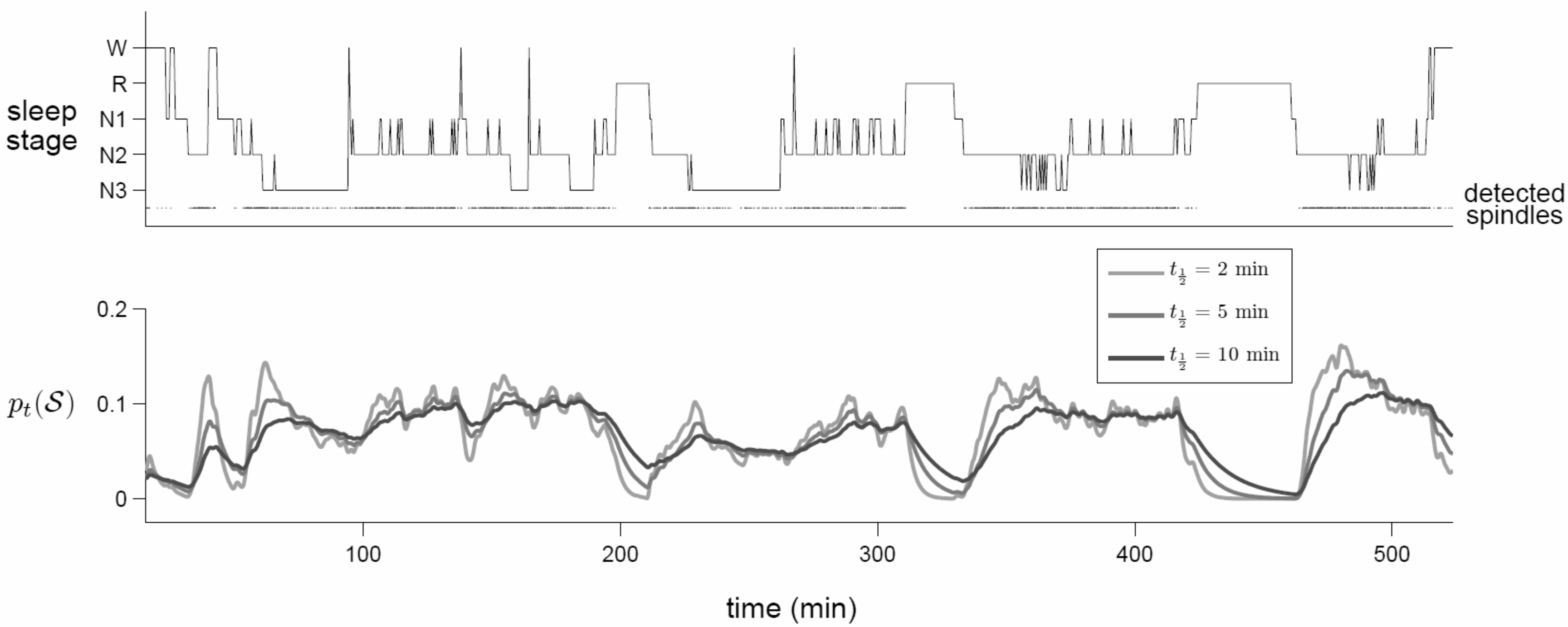


Basner *et al.* Aircraft noise effects on sleep: Mechanisms, mitigation and research needs, in *Noise and Health, April-June 2010, 12:47, 95-109.*

*A **D**ata-Dr**i**ven **Ba**yesian (**DiBa**) Algorithm for Sleep Spindle Detection*

- Motivation:
  - Standard algorithms extract arbitrary, user-defined features (e.g. 10.5-15 Hz activity)
    - Their output is not intrinsically meaningful
  - More sophisticated, nonlinear algorithms are computationally complex
    - Can t been implemented in real time
- Approach:
  - KL transform (PCA)
  - Bayesian Inference

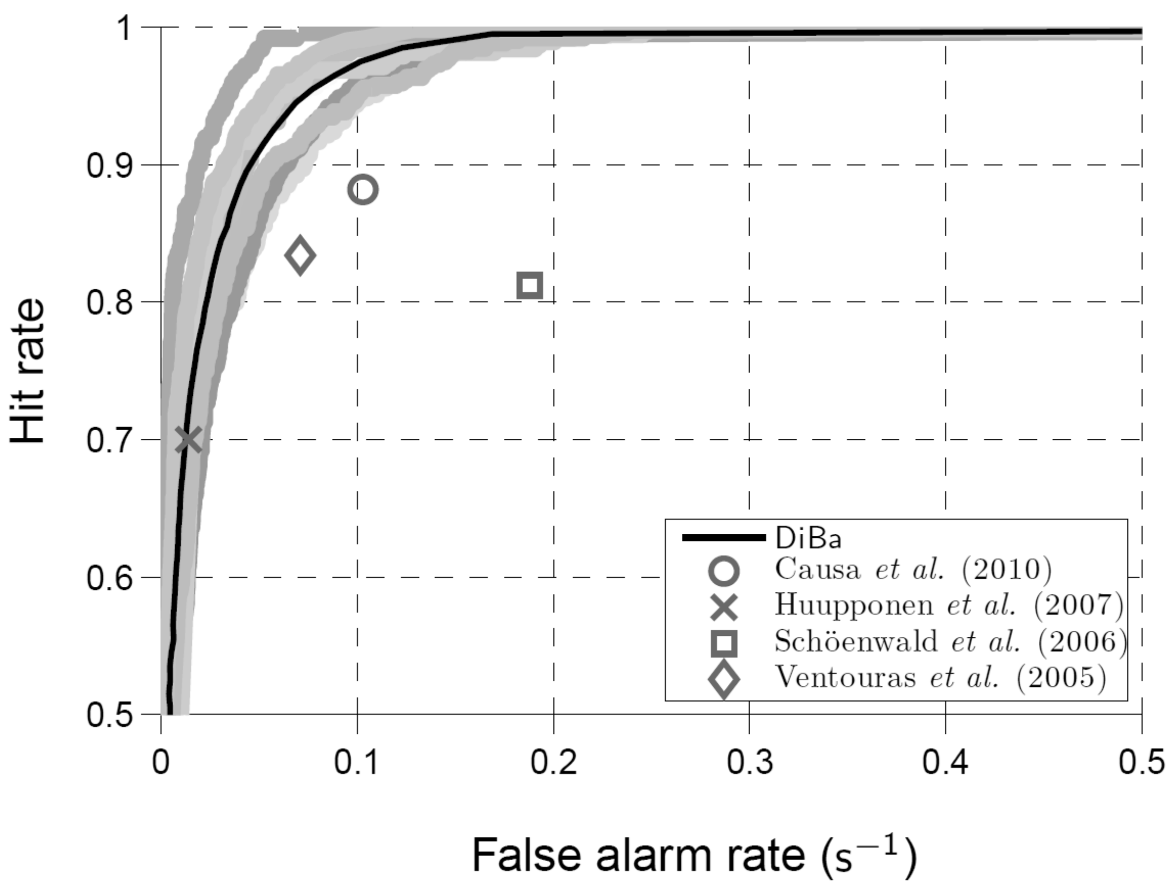
An All-night Setting



Performance Analysis

- N = 8 subjects
  - 5 females, 3 males
  - Median age 22 years (range 20-46)
- Rotating, leave-one-out design
- 26 hours of scored sleep data
  - 3875 sleep spindle events
  - All sleep stages
    - 3% N1
    - 45% N2
    - 34% N3
    - 18% REM
- *Hit Rate*: proportion of "true" spindles detected
- *False Alarm Rate*: # of spurious spindles declared per second of spindleless sleep

Performance Analysis



Features of DiBa

- DiBa probes for distinguishing contextual features of the sleep spindle
  - Derived empirically from a large pool of observations from multiple individuals
  - Can be adapted in a straightforward way to new populations
- DiBa produces a "soft" output with intuitive significance
  - The probability of a spindle's presence at each sample of the EEG
  - Interpretation and parameter specification become more transparent
- Low computational complexity
  - Suitable for online implementation

Circadian Biology