Sleep Disorders: Identifying Biomarkers and Clinical Applications

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2017

Illnesses in Gulf War Veterans

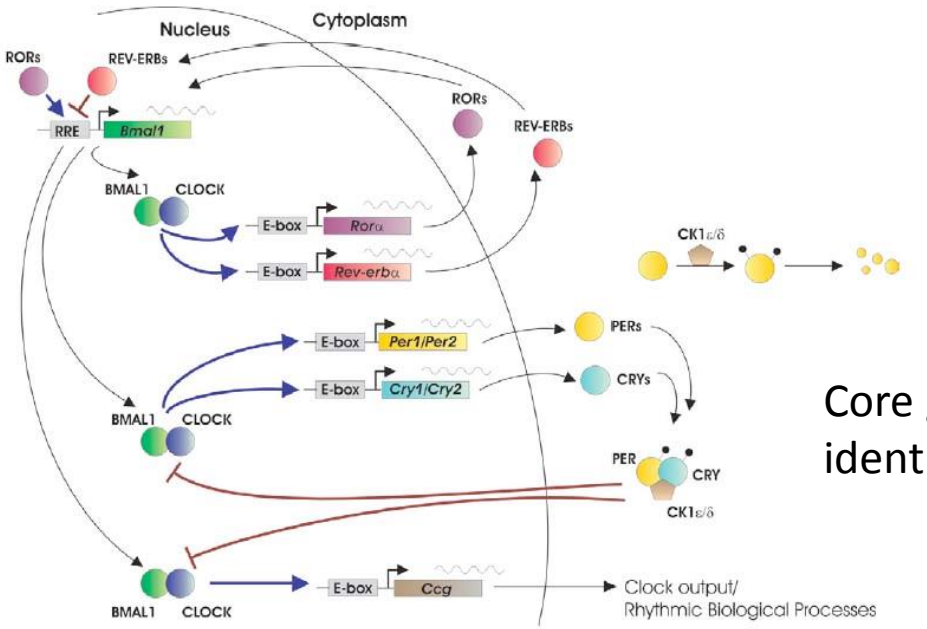
- Complex set of symptoms that most resemble Chronic Fatigue Syndrome or Fibromyalgia:
  - fatigue, memory loss, sleep disturbances, joint pain, rash with depression/anxiety
- Sleep disorders such as insomnia, unrefreshing sleep are prevalent; in one small study mild sleep disorder breathing was found more frequently vs controls
- Psychological (anticipation, PTSD) and physical (desert, physostigmine, vaccines, CW, oil wells etc.) exposure were numerous, but none are constantly associated with illness
- No clear physical or biochemical abnormality. No consistent explanations, most agree it may be multifactorial
- Ascertainment/study results likely biased due to media attention

Why Study Sleep?

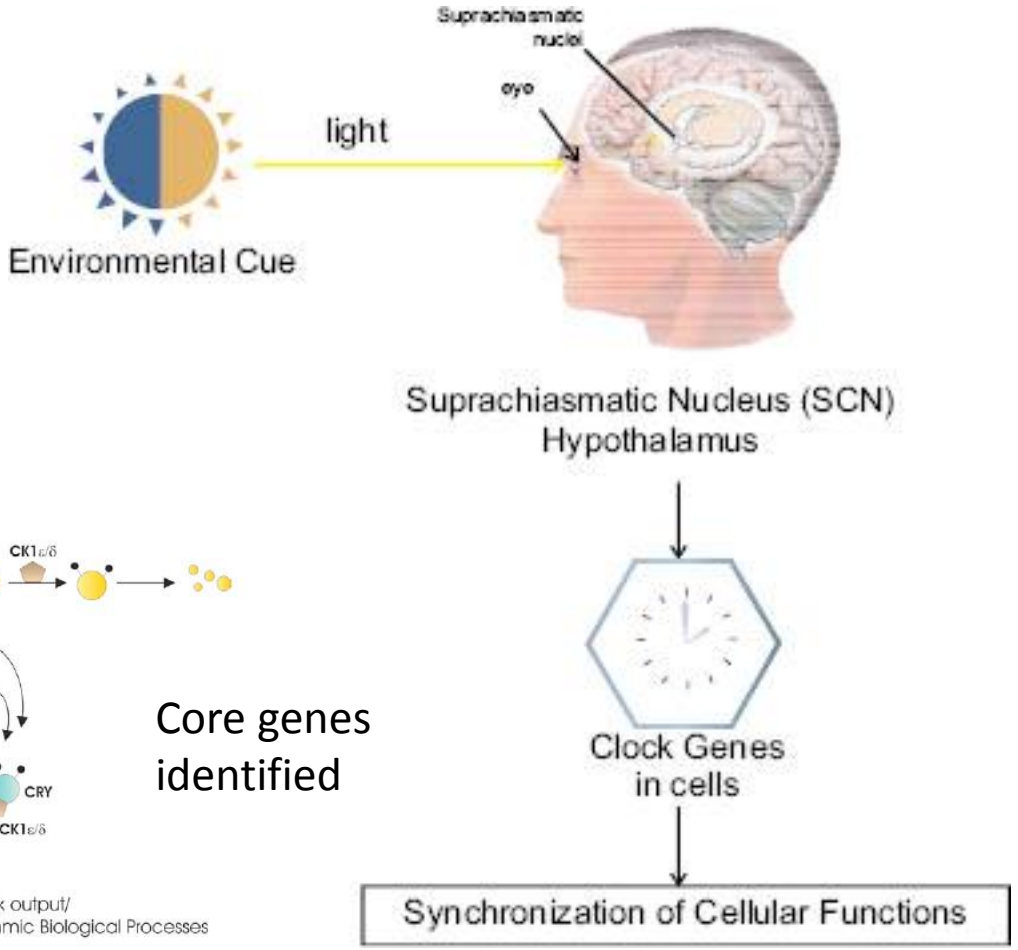
- Opportunity for major discovery: why we sleep is one of the last remaining biological mysteries.
- 70 million Americans complain of sleep problems:
  - ✓ Sleep apnea (~20%)
  - ✓ Insomnia (~10%)
  - ✓ Restless Legs Syndrome/Periodic Leg Movements (~3%)
  - ✓ Hypersomnia/Fatigue/Narcolepsy (~4%)
- Technology now exists to objectively analyze sleep data in ways that were previously impossible
- Move toward home based technology and therapies

Circadian Clock mechanisms well understood

4,256/7497=57% of genes are cycling
Zhang R, et al. Proc Natl Acad Sci U S A. 2014.

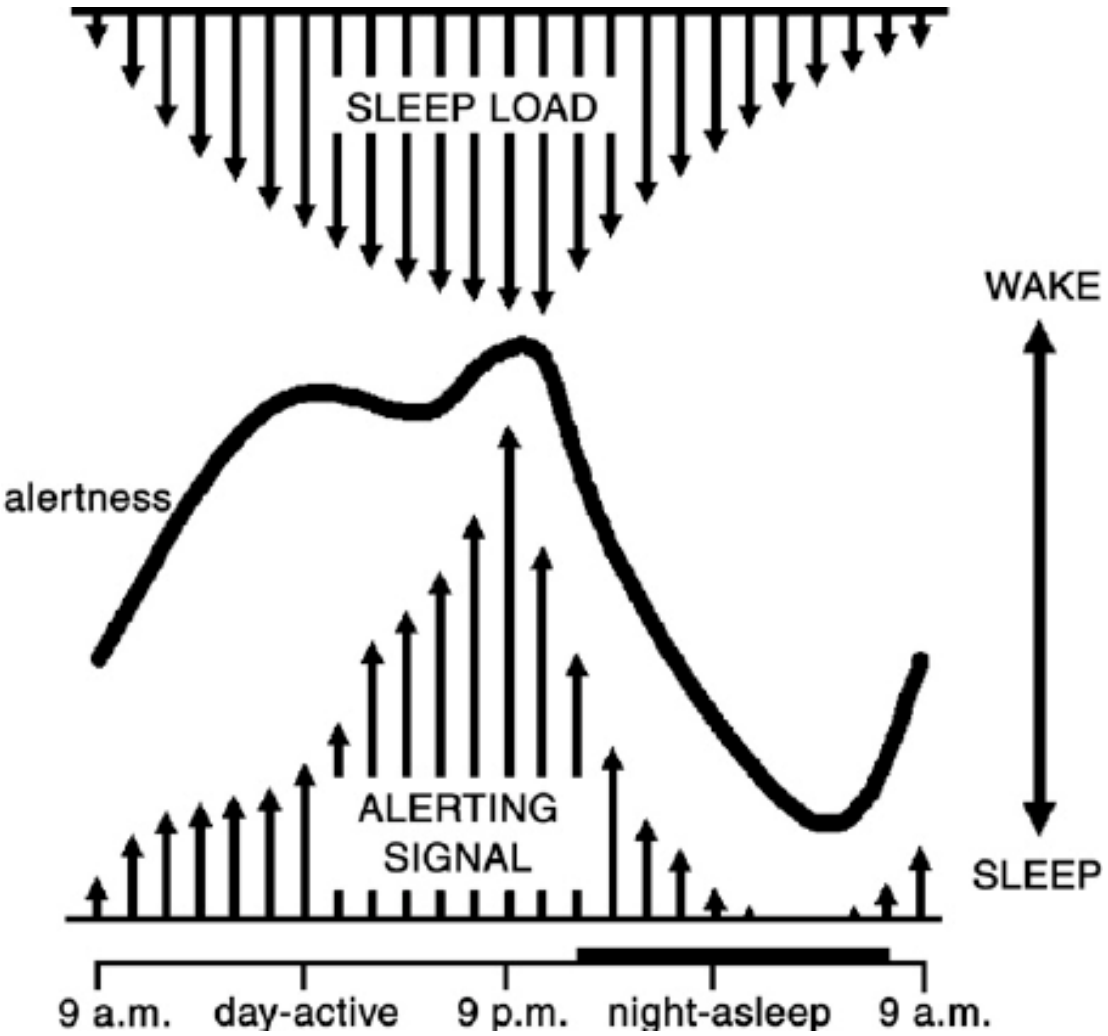


Core genes identified



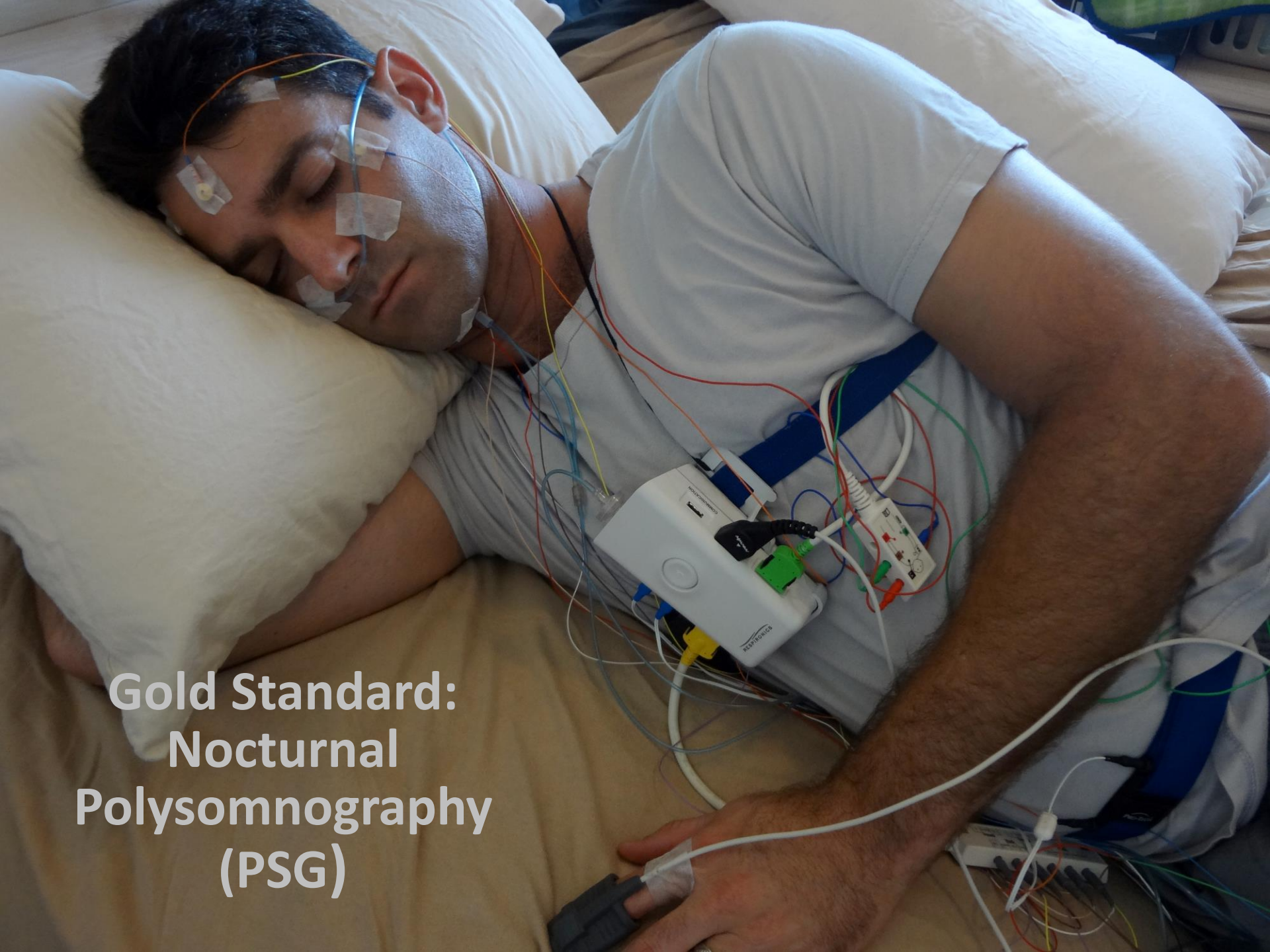
Sleep Homeostasis mechanisms not understood

- Sleep and circadian physiology interact to maintain wakefulness during the day and control sleep during the night
- In the cortex and hypothamus combined, 4811/11078=43% of genes are sleep debt dependent, with about 1,520 (13%) sleep debt specific (Mackiewicz et al, Physiological Genomics, 31(3): 441-457, 2007)
- No Core gene identified

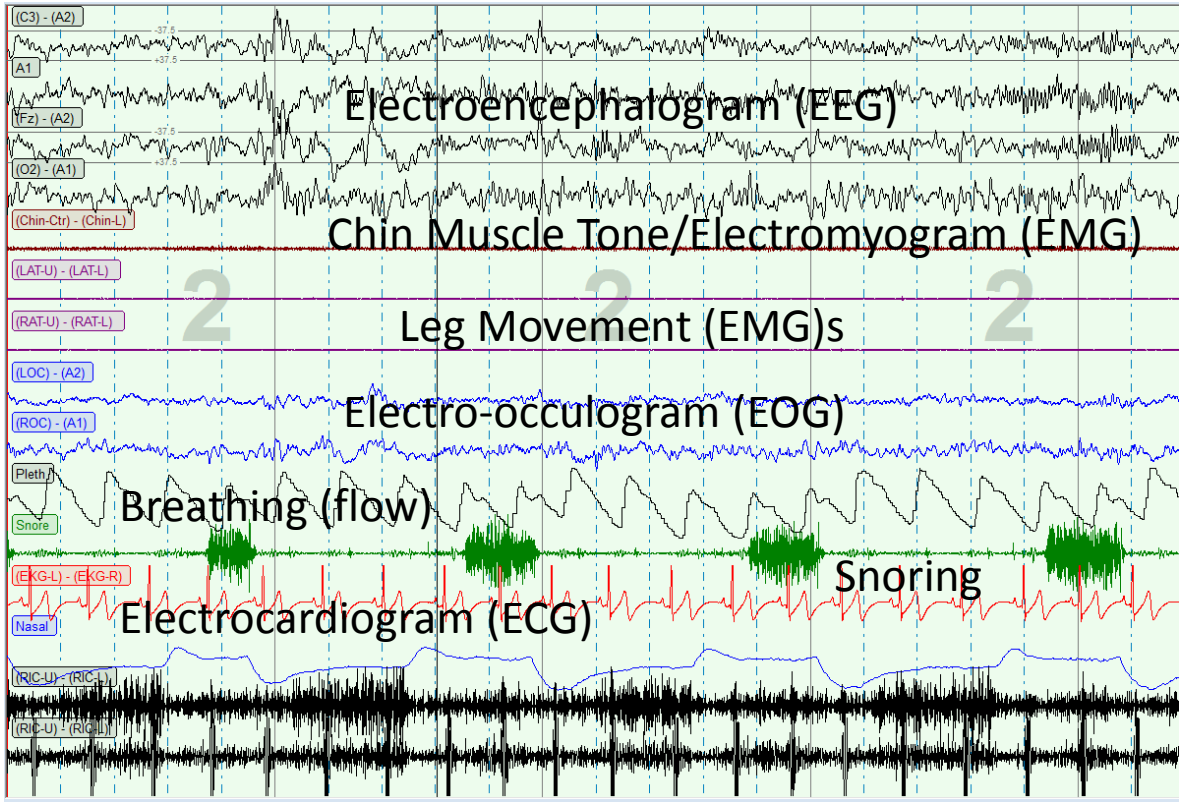


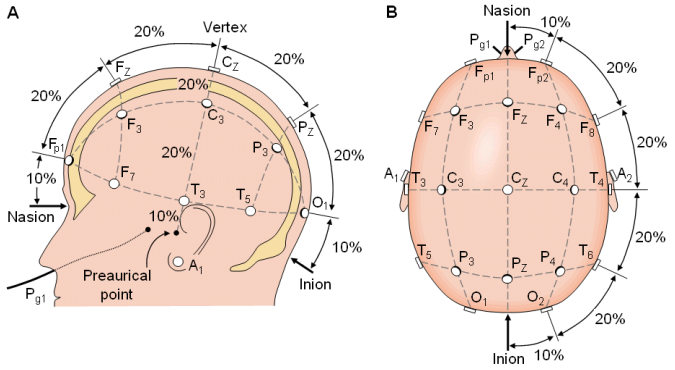
Sleep Disorders

- Obstructive sleep apnea (~20%)
  - ✓ Sleepiness
  - ✓ Cardiovascular risk
- Insomnia (~10%)
  - ✓ Poor quality of life
  - ✓ Anxiety/Depression
- Restless Legs Syndrome/Periodic Leg Movements (~3%)
  - ✓ Depression
  - ✓ Cardiovascular risk
- Hypersomnia/Fatigue/Narcolepsy (~4%)
  - ✓ Link of long sleep with Bipolar disorder/Schizophrenia

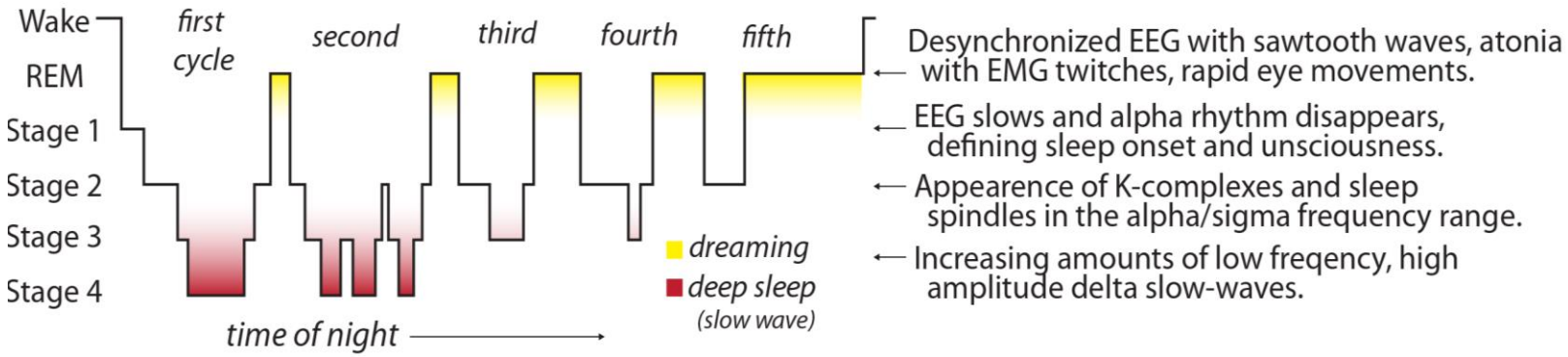

Gold Standard:
Nocturnal
Polysomnography
(PSG)

Gold Standard: Nocturnal Polysomnography (PSG)





Sleep hypnogram for one night of sleep



Critical needs in the field and how we are solving them

- There is no single “on line” questionnaire that assess sleep habits and subjective sleep symptoms for all disorders
  - ✓ The field is still fragmented by discipline, with questionnaires that have been validated only in the context of single, pure sleep disorders populations
  - ✓ Creation of the on line Alliance Sleep Questionnaire (ASQ) and associated App
- Need for better analytics of PSG signals
  - ✓ Currently only summary statistics such as sleep stages, sleep efficiency, the Apnea Hyponea Index (AHI), periodic Leg movement Index (PLMI), REM sleep latency are provided, all scored by humans
  - ✓ Use of machine learning to reveal new biomarkers
- Need for better ‘at home” data collecting systems but what sensors should they have?
  - ✓ EEG, triaxial accelerometer, O2 sat, transcutaneous or expiratory Co2, snoring sound, cardioballistography, nasal or oral pressure cannula, Respiratory belts, EMG, Photo Pletysmography (PPG), EKG etc
- Need for biological biomarkers
  - ✓ Could we find biological markers of sleep disorders, hypoxia (sleep apnea), sleep deprivation/debt, circadian phase?
  - ✓ Genetics and proteonomics
- Need for at home, on line interventions with monitoring
  - ✓ cBTI on line
  - ✓ EEG with feedback therapies (rythm)

Alliance Sleep Questionnaire (ASQ) Taskforce

Stanford University

Harvard University

Emmanuel Mignot, Chair
Jim Walsh, Co-chair
Laura Barger
Ruth Benca
Chuck Czeisler
Janine Hall
Pam Hyde
Clete Kushida
Eileen Leary
Greg Maislin
Allan Pack
Paul Peppard
Shantha Rajaratnam
Sharon Schutte-Rodin
Meredith Rumble
Shannon Sullivan

St. Luke's Hospital

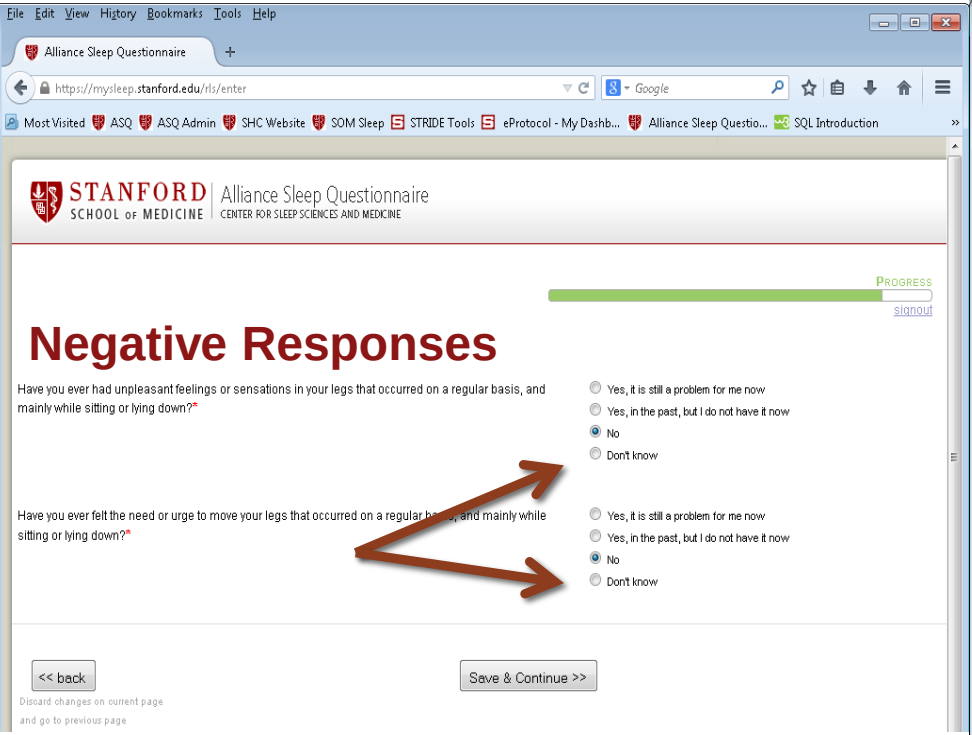
University of Wisconsin-Madison

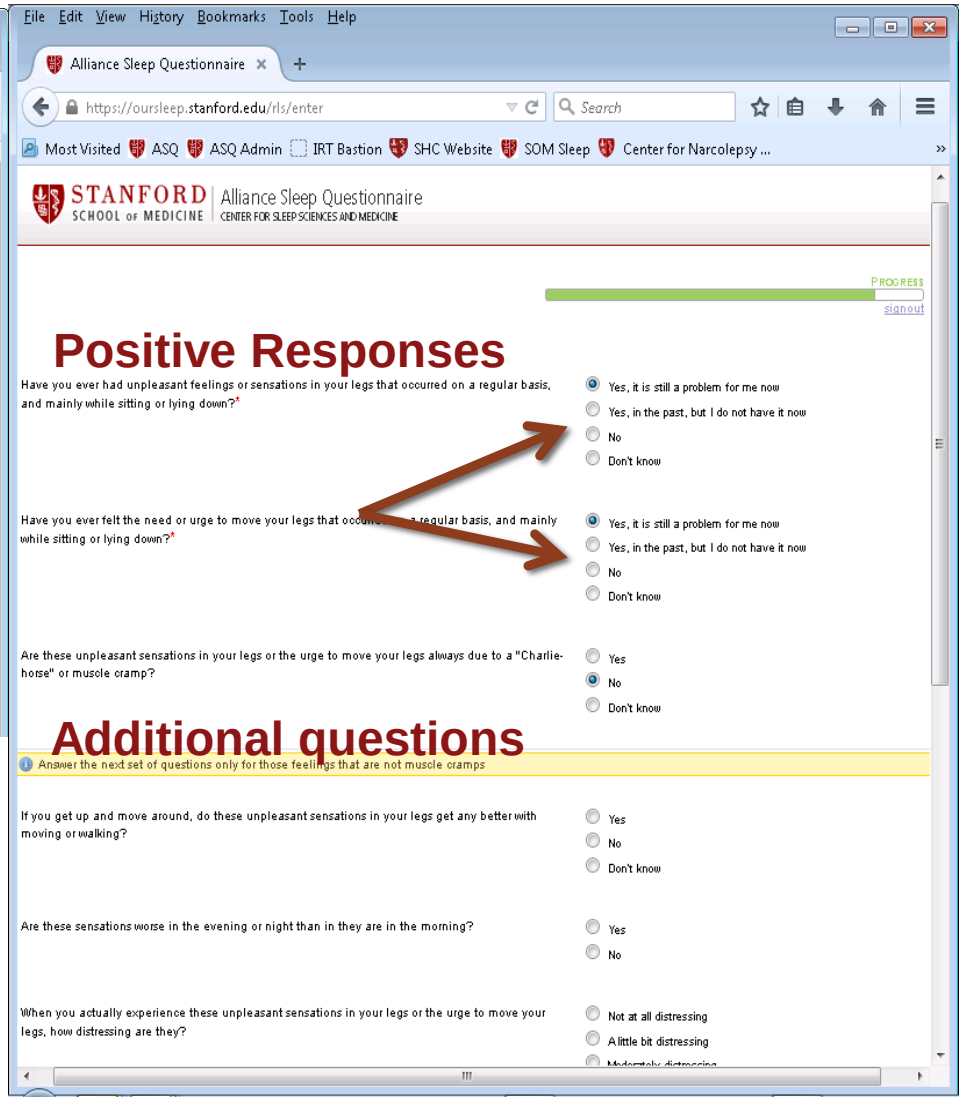
University of Pennsylvania

Many others as consultants

ASQ Uses Branching Logic:

Restless Legs Syndrome Section





ASQ Report

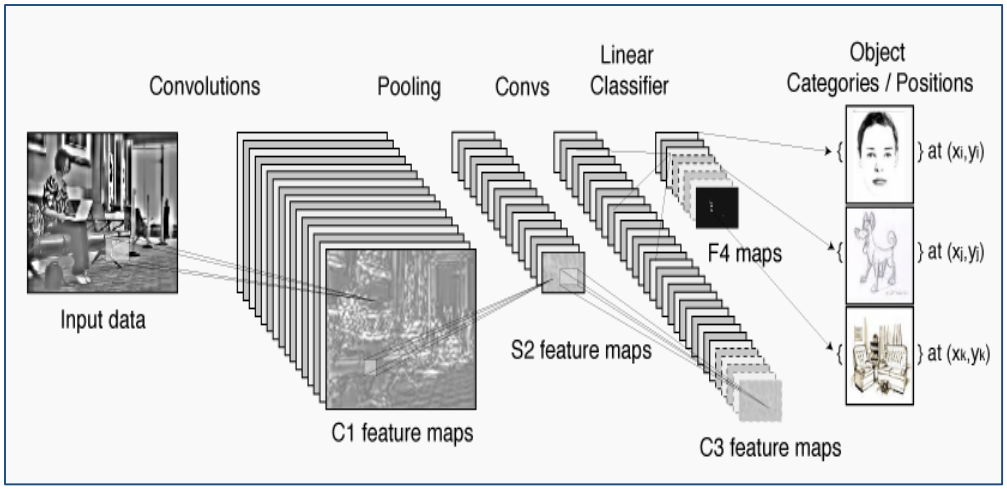
Insomnia Symptoms:			Test, Full, MRN n/a
Insomnia Scale (ISI):	28	**Meets ISQ diagnostic criteria:**	No
Difficulty falling asleep:	Very severe	**Problems waking too early:**	Very severe
Difficulty staying asleep:	Very severe	**Frequent wakenings:**	Always (5-7 times per week)
Satisfaction with current sleep pattern:	Very dissatisfied	**Extent prob interferes with daily functioning:**	Very much interfering

Restless Legs Symptoms:			Test, Full, MRN n/a
Current Probability:	Unlikely	**Current Severity Level:**	Not applicable
Limb discomfort/ unpleasant sensation while sitting/ lying down:	Yes, it is still a problem for me now	**Frequency of symptoms:**	n/a
Urge to move with relief upon movement:	Yes, it is still a problem for me now	**Level of distress:**	n/a
Unpleasant sensations assoc with muscle cramps:	Don't know	**Age of onset:**	5
Began with pregnancy:	n/a	**Ended with same pregnancy:**	n/a

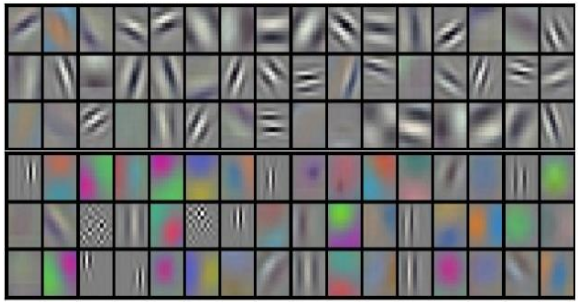
(validated in about 10,000 subjects @ Stanford sleep clinic)

Improved PSG analytics: Machine learning Convolutional Neural Network (ConvNet)

- A supervised prediction model in which the input data is low-level e.g. an image or a spectrogram.
- Features are constructed through a network of filter and subsampling layers.
- Deeper networks may construct more complex features.
- Resulting features depend on input data, as parameters change iteratively during training.
- Often used in computer vision or speech recognition tasks.



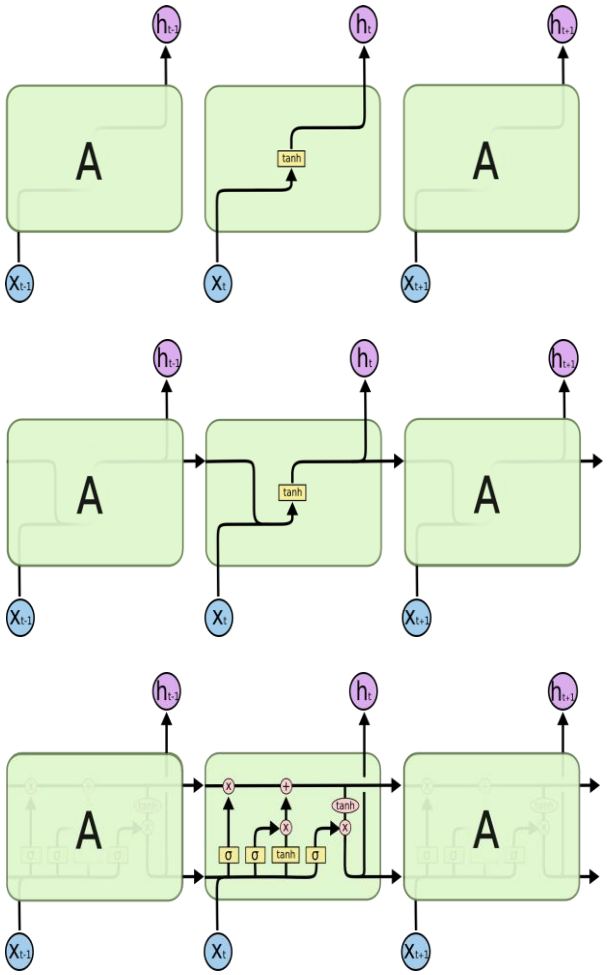
Example borrowed from: http://www.computervisionblog.com/2015/03/deep-learning-vs-machine-learning-vs.html



Example borrowed from: http://cs231n.github.io/convolutional-netwrks/

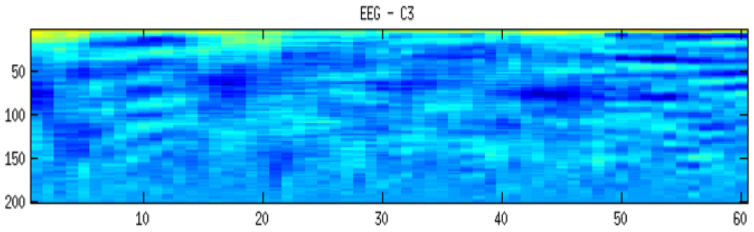
Machine Learning

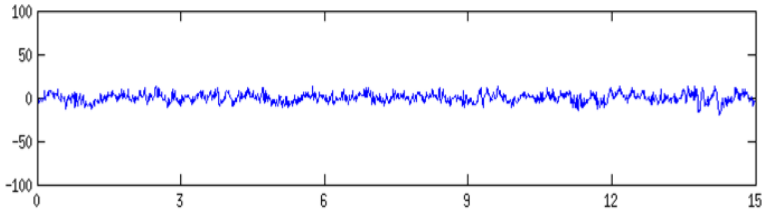
- Feed-forward neural network (FFNN):
  - Process each observation independently
- Recurrent neural network (RNN):
  - Introduces a temporal dimension
  - Used to model change in frequency
- Long Short-Term Memory (LSTM) network
  - Introduces support for long-term dependencies
  - Context-aware decisions



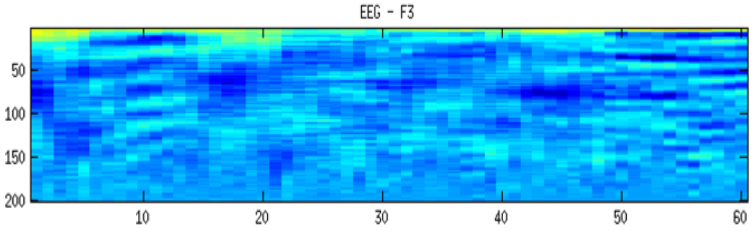
Sleep data representation. Overlapping autocorrelations: Wake

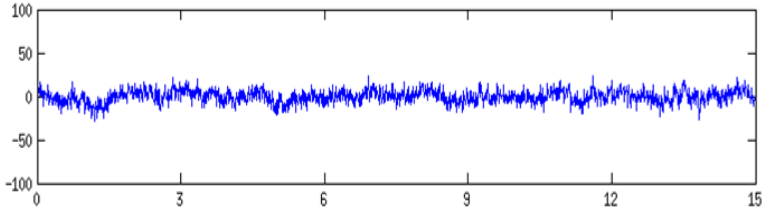
EEG - C3



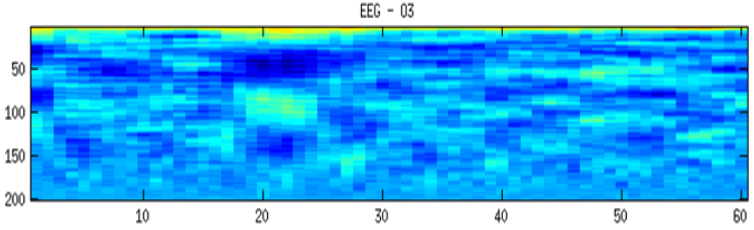


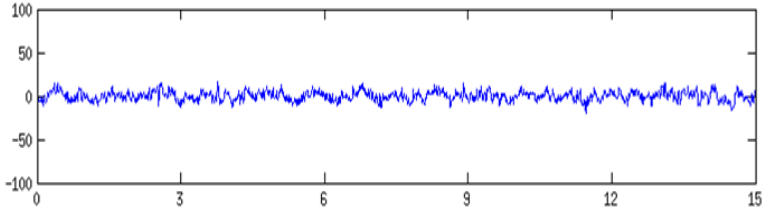
EEG - F3



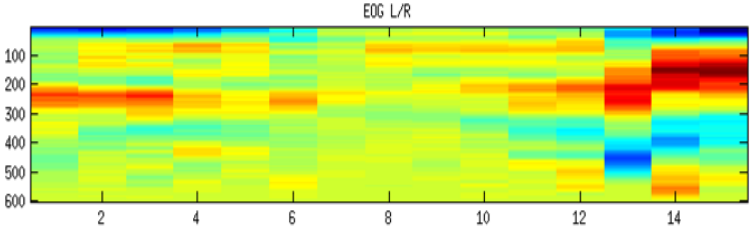


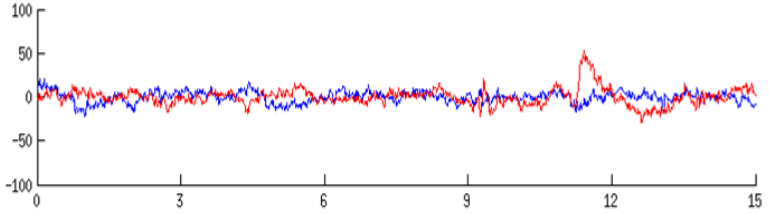
EEG - O1



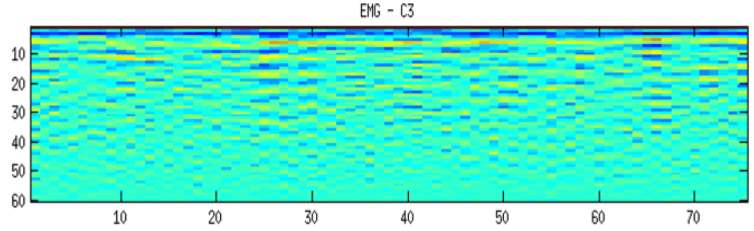


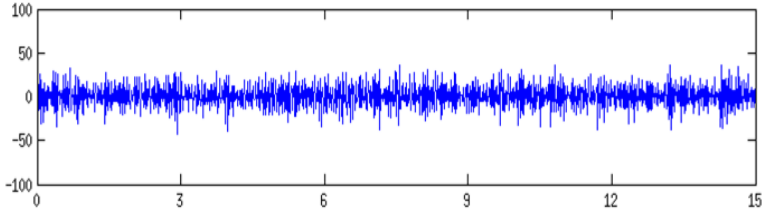
EOG



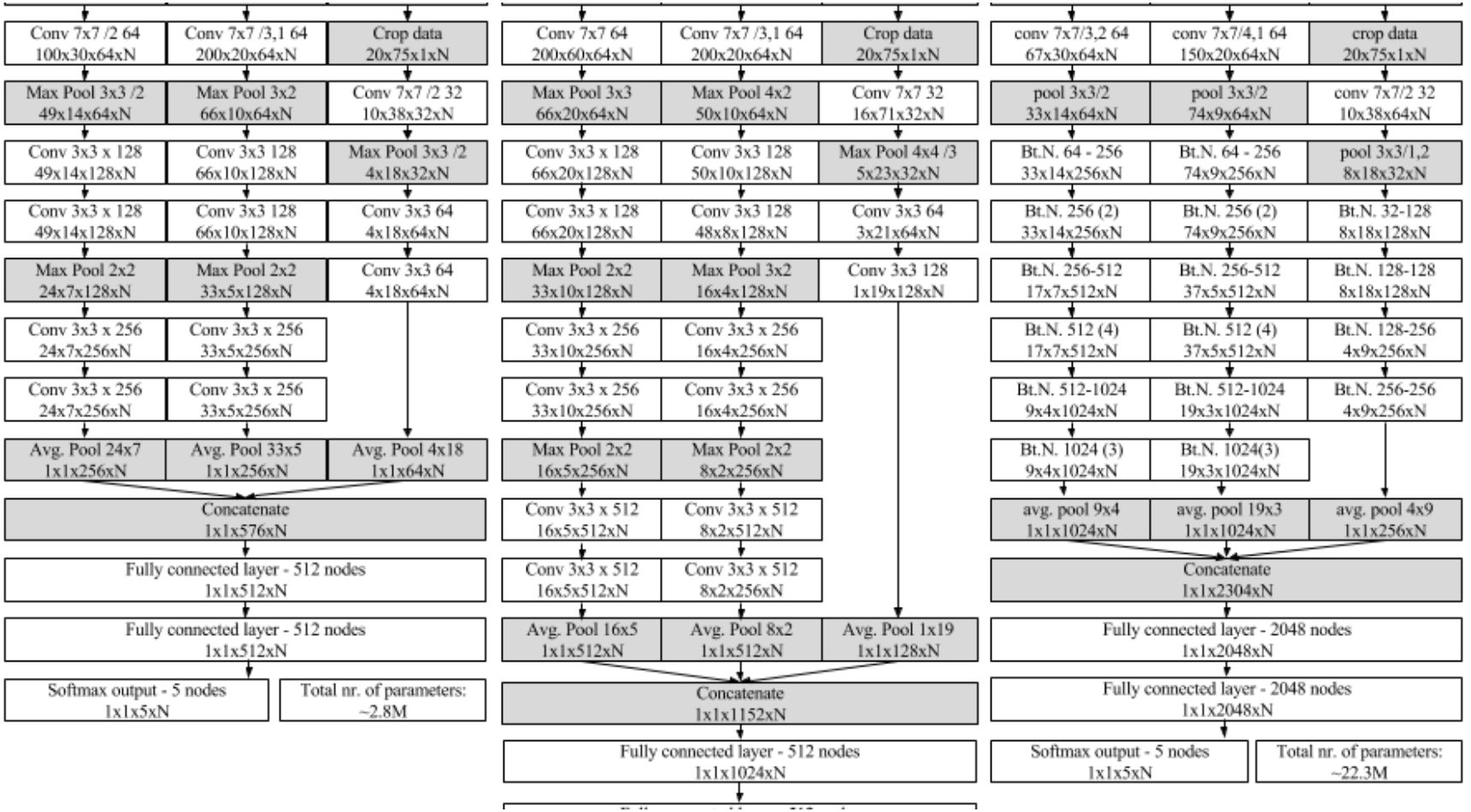


EMG - Chin





Three networks models are used



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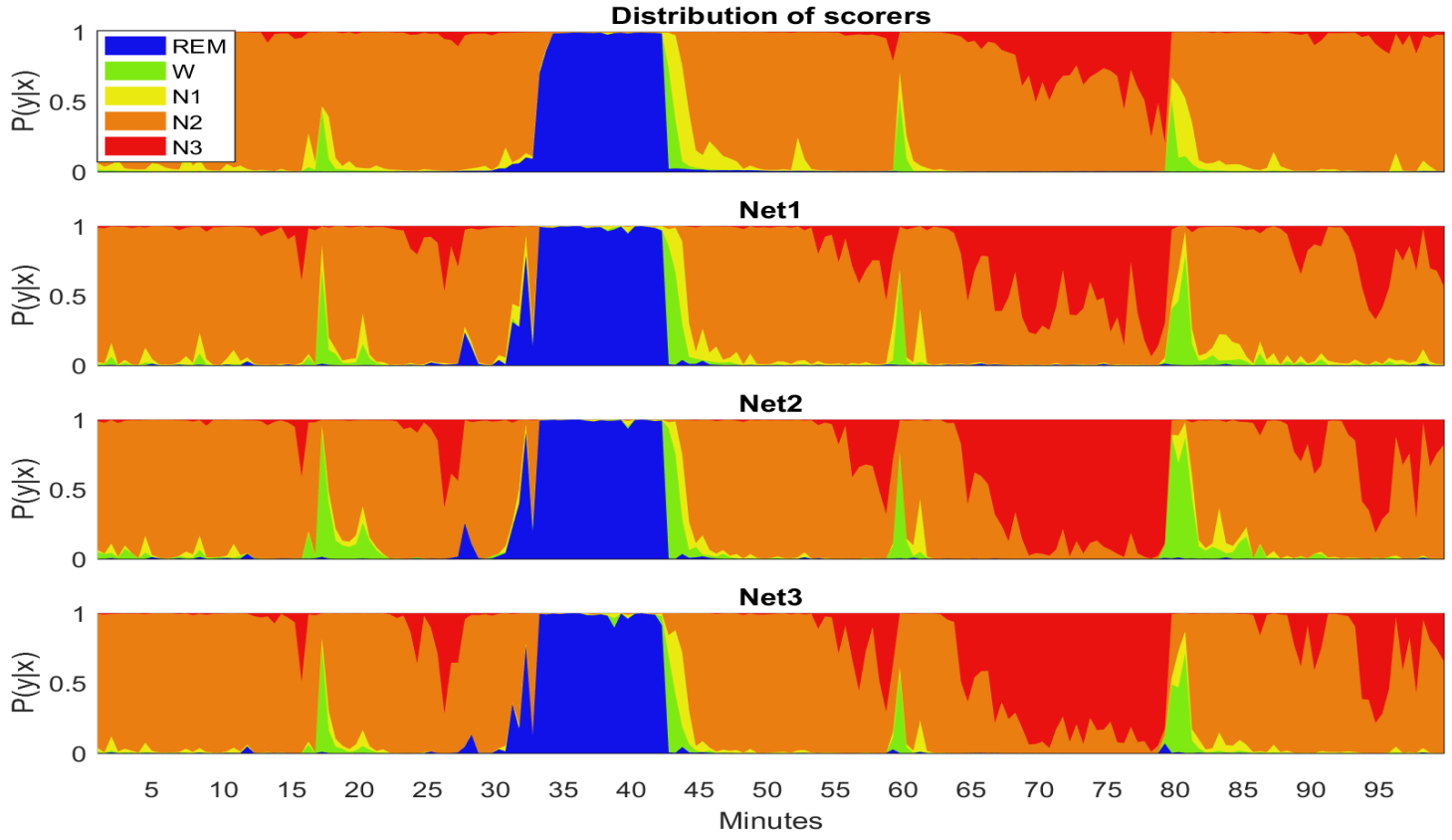
Comparaison with the AASM Inter-Scorer Reliability

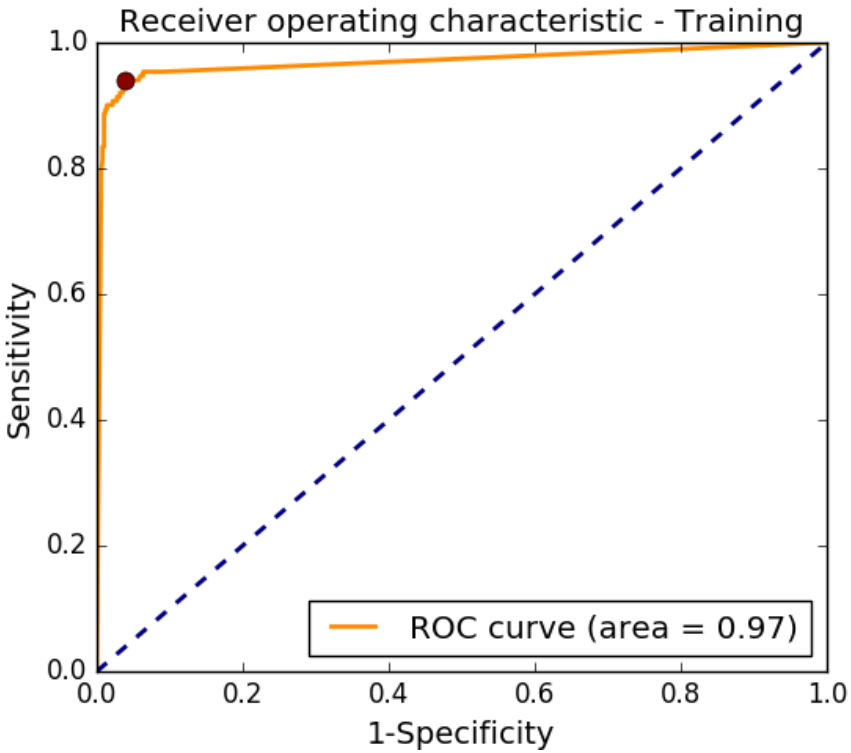
Performance of networks used

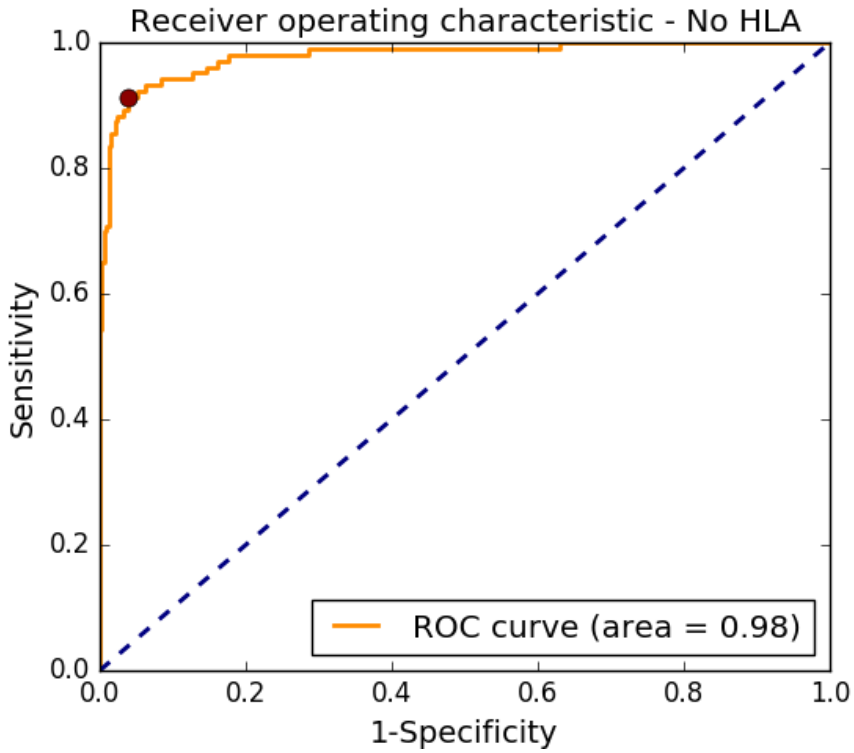


Selection of narcolepsy features using Lasso regression

#	Description	Relative importance
1	REM latency (Automatically extracted)	1
2	Mean co-occurence of REM and wake	0.80
3	Mean value of REM x the time till 10 % of the cumulative fraction of REM is reached.	0.68
4	The maximum value of co-occurrence of N2 and REM.	0.66
5	The mean value of N2 x the time till 10 % of the cumulative fraction of N2 is reached.	0.61
6	Time till 10 % of the cumulative fraction of the co-occurrence of all 5 stages is reached.	0.55
7	Mean value x the Shannon entropy of the co-occurrence of N2 and N3.	0.40
8	Time till 10 % of the cumulative fraction of the co-occurrence of N1 and N2 is reached.	0.37
9	Maximum value of co-occurrence of wake and N1	0.36
10	Maximum value of co-occurrence of wake and REM	0.35

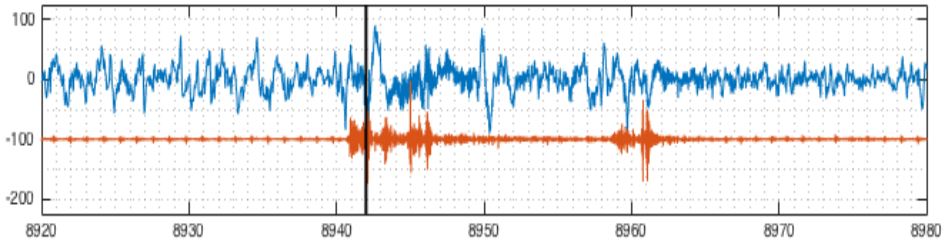
Validation to diagnose narcolepsy

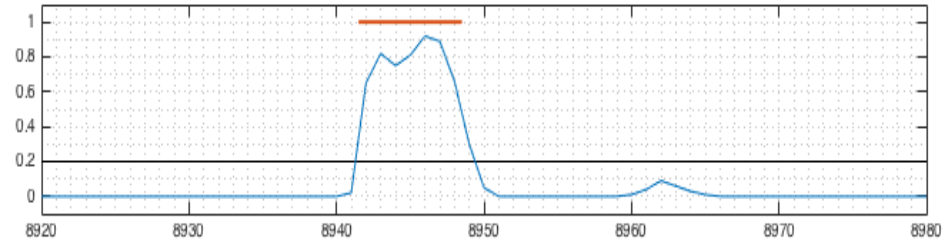


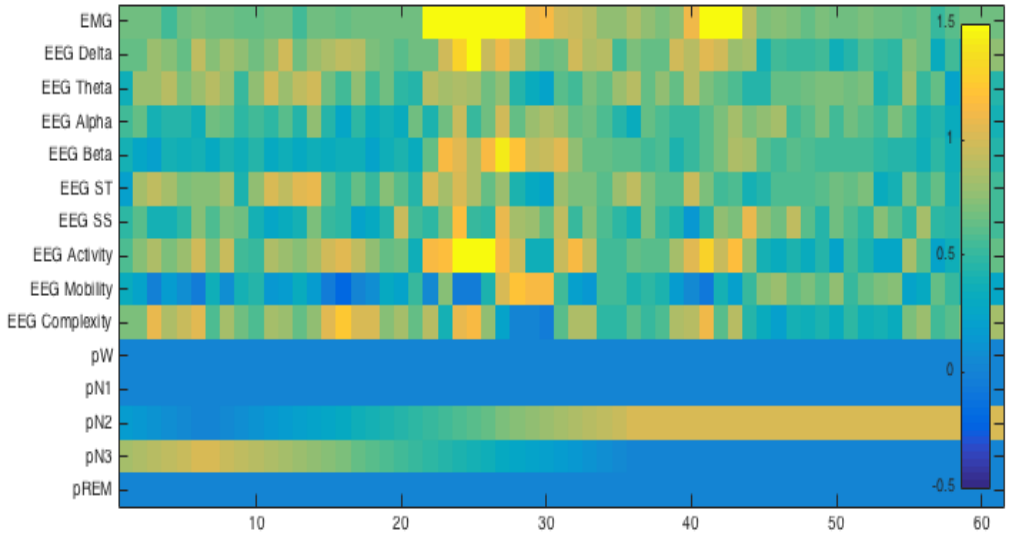


Stephansen et al., in preparation

LSTM detection of arousals







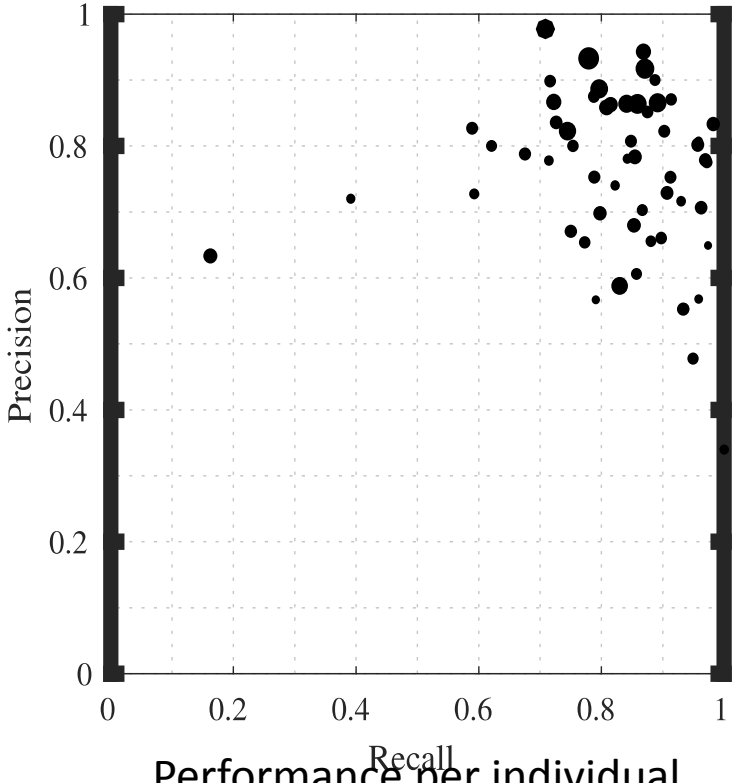
OVERALL

Precision = 0.76

Recall = 0.82

F1 = 0.79

auPR = 0.84



Performance per individual (dot size=n observation)

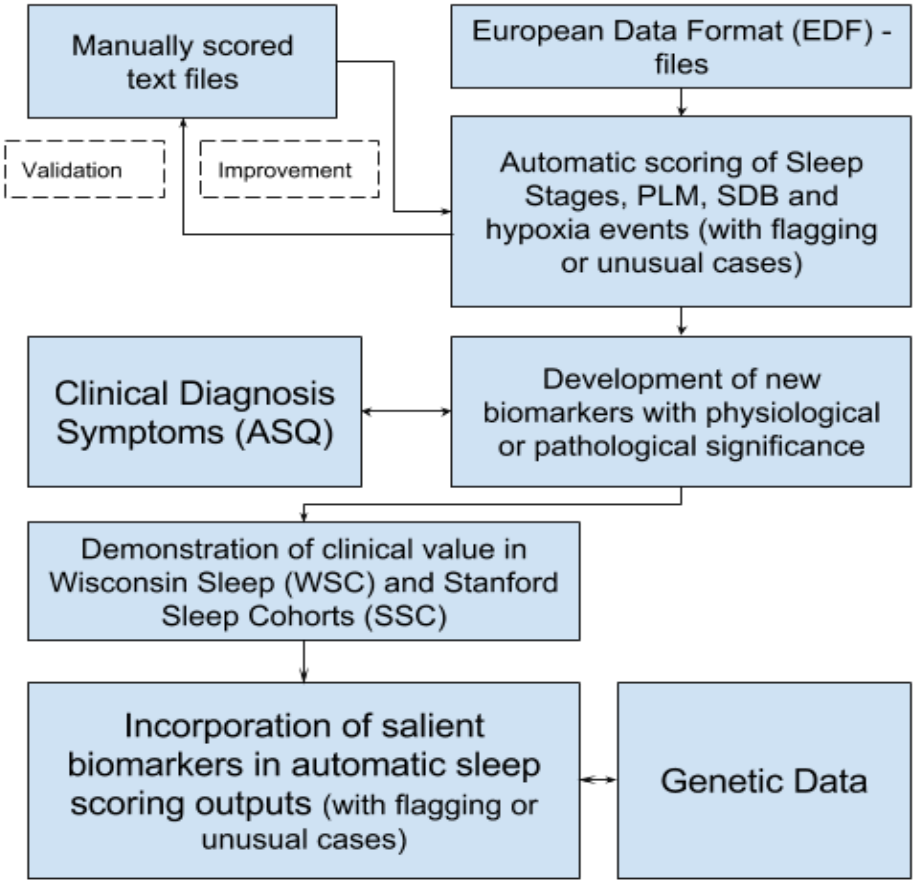
Goal 1: A single, multimodal PSG analyzer

- Doing classic and novel sleep stage identification
- Detecting macro and microarousals (autonomic and EEG)
- Detecting all breathing abnormalities during sleep, including subtypes of sleep apneas
- Detecting periodic leg movements during sleep, including subtypes
- The detector would reveals a complex muti-dimensional phenotype for each individual
- To apply in the context of the Stanford Technology Analytics and Genomics of sleep (STAGES) study

Need to Measure Phenotypes Across Disciplines

Insomnia, hypersomnia/narcolepsy, and psychiatric comorbidity	• EEG power spectra features per sleep stage* • Delta power during wake, Slow Wave Sleep during sleep corrected for habitual sleep amounts • Hilbert Huang Transform analysis of the EEG (see letter of support of Dr. Huang) † • Sleep stage transition analysis* • Sleep stage space analysis and automatic sleep/wake scoring by 10 sec epochs* • Slow wave/delta power dynamics across the night and sleep cycle analysis • Coherence analysis (inter- and intra- hemispheric, per sleep stage) • Microarchitecture analysis (spindles*, k-complex, saw tooth waves detection) • REM sleep features (REM density, REM sleep atonia)* • Microarousal detections out of various sleep stages† • Measures of circadian phase through analysis of all signals in correlation with body temperature†
RLS and PLMs (may predispose to depression and cardiovascular disease)	• PLMI, periodicity index, dynamics across the night and by sleep stage, with and without arousal (frequency of PLMs)* • Time locked analysis of EEG, EMG, ECG locked on PLM (impact of PLMs)*
Sleep disordered breathing (SDB) (predisposes to cardiovascular disease and sleepiness)	• Apnea Hypopnea Index and other derivatives (by sleep stage, with various definitions with and without oxygen desaturation and arousal, central or obstructive) (frequency of respiratory events)* • Time locked analysis of Oxygen saturation, EEG, EMG, ECG locked on SDB events per sleep stage (severity of respiratory events)* • Oxygen saturation at baseline and end of the night, per sleep stage, time spent at various levels of Oxygen saturation* • Breathing frequency, inspiration and expiration time per sleep stage†
Parkinson's disease early biomarkers	• REM sleep without atonia* • Sleep fragmentation, loss of spindles* • ECG-power spectra changes across sleep stages*
Alzheimer's disease early biomarkers	• Power spectra in REM sleep* • Coherence analysis
Seizure activity during sleep	
ECG	• Analysis of shape, PR, QT, arrhythmia, and conduction defects across sleep stages

Analytical Flow Chart of large scale PSG analysis

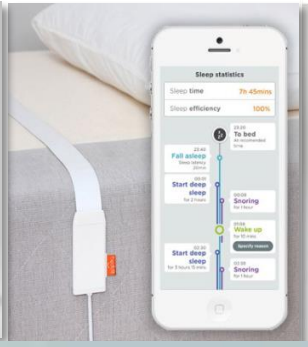


The whole thing is more than the sum of its parts –
tell me, is that your feeling only or more than that?

Dirk Meissner

Goal 2: A simplified, usable portable PSG system

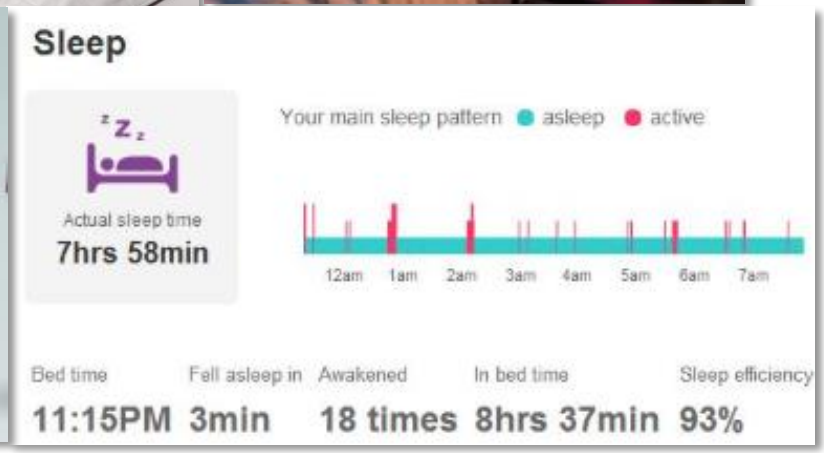
- The brain during sleep is going through an automatic program uninfluenced by sensory inputs and motor activity
- We believe that longitudinal studies could be method to check brain health periodically
- What minimal number of sensors must be included to capture all the useful information a full PSG can provide
  - old markers such as AHI, new markers like EEG biomarkers of depression or neurodegenerative disease
- Must be portable and confortable
- Signals could be sent over the internet and automatically processed
- Potentially, feedback could be given to subject to correct abnormality (like for CBTi)



Whitings Aura pad

Basis

Fitbit



Consumer Sleep Tracking Devices

Confortable EEGs

Showing results for "sleep apps"

iPhone Apps

Sleep Cycle alarm clock
Health & Fitness
$0.99
In-App Purchases
Essentials

Sleep Pillow Sounds: white...
Health & Fitness
Get

Relax Melodies: Sleep zen sound...
Health & Fitness
Get

iHome+Sleep, the alarm clock app...
Utilities
Get
In-App Purchases

Alarm Clock Free
Utilities
Download

Alarm Clock HD - Free
Utilities
Get

White Noise Lite: Relax. Sleep....
Health & Fitness
Get

Sleep Machine Lite
Productivity
Get

Free Relaxing Sounds Of Natu...
Health & Fitness
Get
In-App Purchases

Sleep Pillow Sounds: white...
Health & Fitness
$1.99

Applets
Utilities
Get
In-App Purchases

Alarm Clock 4 Free
Utilities
Get
In-App Purchases

Rain, Rain Sleep Sounds
Health & Fitness
Get
In-App Purchases

Relax & Sleep Well by Glenn...
Lifestyle
Get
In-App Purchases

Sleep Time : Sleep Cycle Smart Alar...
Health & Fitness
Get

iDream - Sleep Maker
Lifestyle
Get
In-App Purchases

Brain Wave ™ - 32 Advanced...
Health & Fitness
$2.99

Alarm Clock Pro
Utilities
$0.99

Naturespace: Relax Meditate...
Health & Fitness
Get
In-App Purchases

Sleep Better – Smart Alarm Clo...
Health & Fitness
Get
In-App Purchases

UP - Tracker Required...
Health & Fitness
Download

Voice Recognition – Recorder &...
Business
Get

Sleepmaker Rain Free
Medical
Get

My Baby Today | BabyCenter
Health & Fitness
Get

Weather Clock Free
Lifestyle
Get

Relax Melodies Oriental...
Health & Fitness
Get
In-App Purchases

SleepBot - Smart Cycle Alarm wit...
Health & Fitness
Get

SleepStream 2 Pro: Sleep. Rela...
Lifestyle
$2.99
In-App Purchases

Alarm Clock Sleep Sounds Free:...
Health & Fitness
Get
In-App Purchases

iHome Set
Utilities
Get

Nightstand Central Free -...
Productivity
Get

Relaxing Sounds - Sleep well, relie...
Health & Fitness
Get

Christmas Countdown!
Entertainment
Get

Sleep Machine
Health & Fitness
$1.99

Relax Melodies Premium: Sleep...
Health & Fitness
$2.99

iDream - Dream Interpreter and...
Medical
Get

Silva Relaxation-Relax, Relieve...
Health & Fitness
Get

Alarm Clock Music Free
Utilities
Get

iBabyLog : Baby Breastfeeding...
Medical
Get

White Noise Ambience Lite
Health & Fitness
Get

CBT-i Coach

View More by This Developer

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Released: Jun 05, 2013
Version: 1.0
Size: 33.0 MB
Language: English
Seller: US Department of Veterans Affairs (VA)
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Rated 4+

Compatibility: Requires iOS 4.3 or later. Compatible with iPhone, iPad, and iPod touch. This app is optimized for iPhone 5.

Customer Ratings

Current Version:
★★★★½ 12 Ratings

More iPhone Apps by US Department of Veterans Affairs (VA)

PTSD Coach

Description

CBT-i Coach is for people who are engaged in Cognitive Behavioral Therapy for Insomnia with a health provider, or who have experienced symptoms of insomnia and would like to improve their sleep habits. The app will guide users through the process of learning about sleep, developing positive sleep routines, and improving their sleep

US Department of Veterans Affairs (VA) Web Site ▸ CBT-i Coach Support ▸ Application License Agreement ▸ ...More

iPhone Screenshot

The STAGES study: Genetics and Technology in 30,000 subjects

Supplementary sleep data

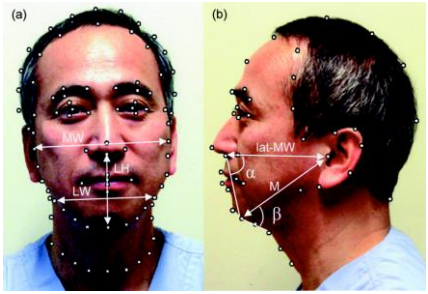
- Sleep schedule evaluation by actigraphy
- Sleep anatomy evaluation by photography

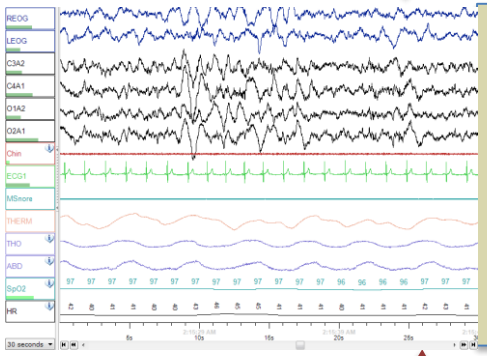
Subjective sleep data (ASQ)

- Sleep habits
- Sleep symptoms (e.g. sleepiness)
- Sleep Disorders (insomnia, OSA, Restless leg syndrome, narcolepsy, parasomnia)

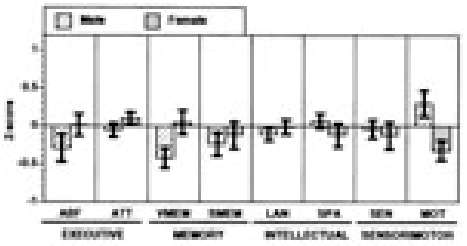
Computerized Neurocognitive Battery (CNB)

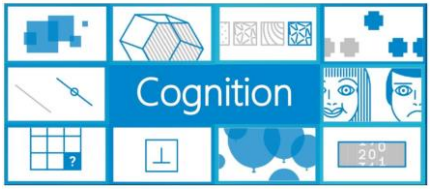
- Attention, executive functions
- Performance Vigilance Tests



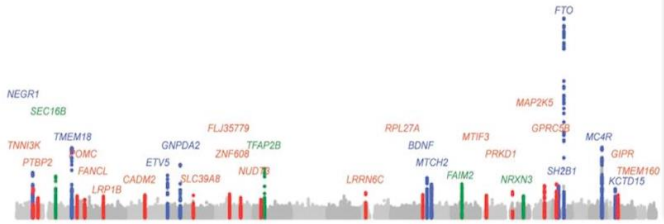


Objective Sleep Nocturnal Polysomnography (Sleep analytics, Machine learning)





Open source



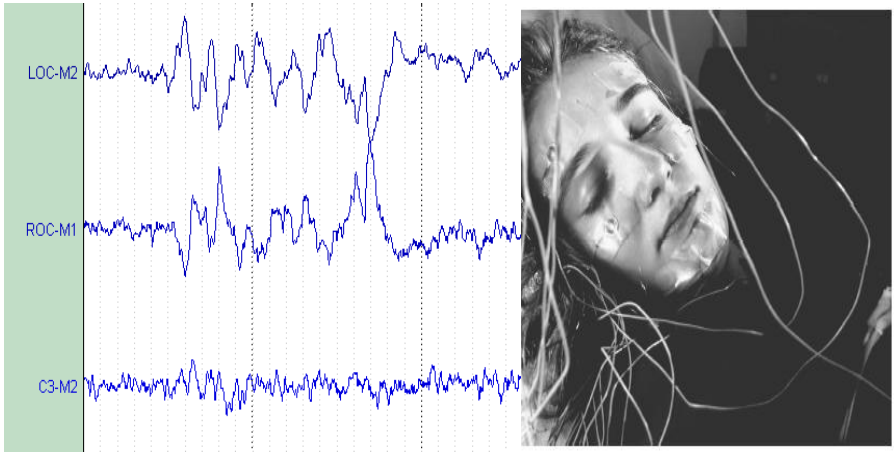
Genetic data
GWAS, sequencing

Why Use Genetic Analysis?

- Genetics and molecular biology are exploding fields and their applications are growing exponentially
- With genetic analysis, it is possible to find the mechanism behind a disease or a physiological process even if there are no clues on where to look
- Once genes and/or pathways have been identified, new treatment strategies and diagnostic tools can be developed

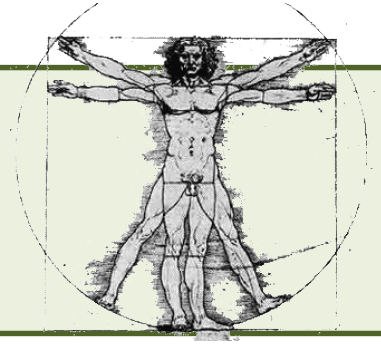
Sleep is an objectively measurable biology with strong genetic effects, therefore it will be tractable by genetic analysis

Sleep Phenotype



Gene Variant (SNP)

Systematic measurement of single nucleotide polymorphisms (SNPs) across the entire human genome.

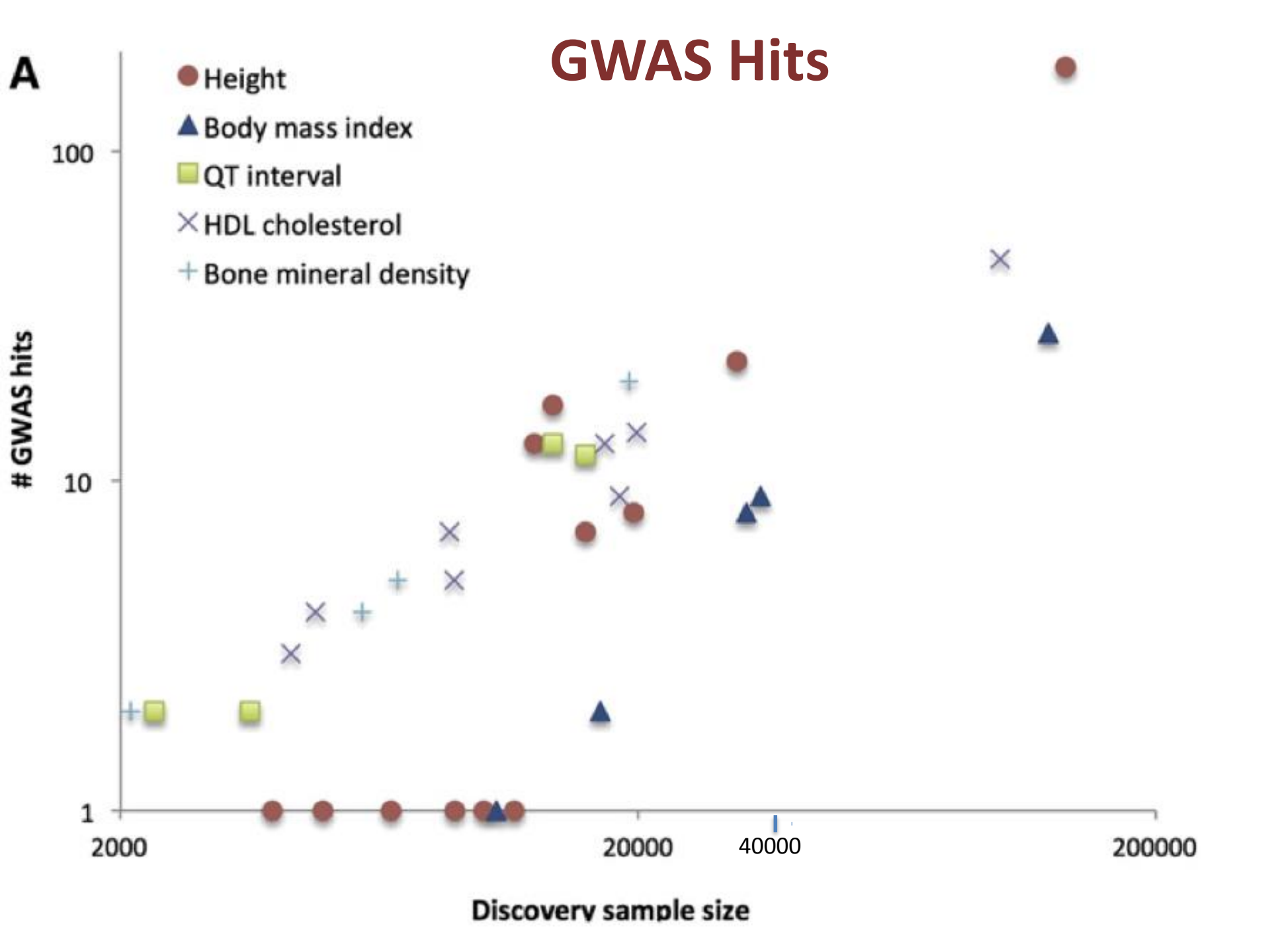


Genome-wide Association Study (GWAS) or Exome / Whole Genome Sequencing*

*Need large sample size

***Need large sample size for genetic studies**

GWAS Hits


A
Height
Body mass index
QT interval
HDL cholesterol
Bone mineral density
100
10
1
GWAS hits
2000
20000
40000
200000
Discovery sample size

Example Of How Genetics Have Been Used To Identify Underlying Genes/Pathways In A Disease Of Unknown Mechanism

Age Related Macular Degeneration (AMD)

Analysis of SNP genotypes across genome indicates pathways

Genes identified

- complement factor H (*CFH*)
- complement component 2 (*C2*)
- complement component 3 (*C3*)
- complement factor I (*CFI*)
- *HTRA1/ARMS2*

Pathway identified

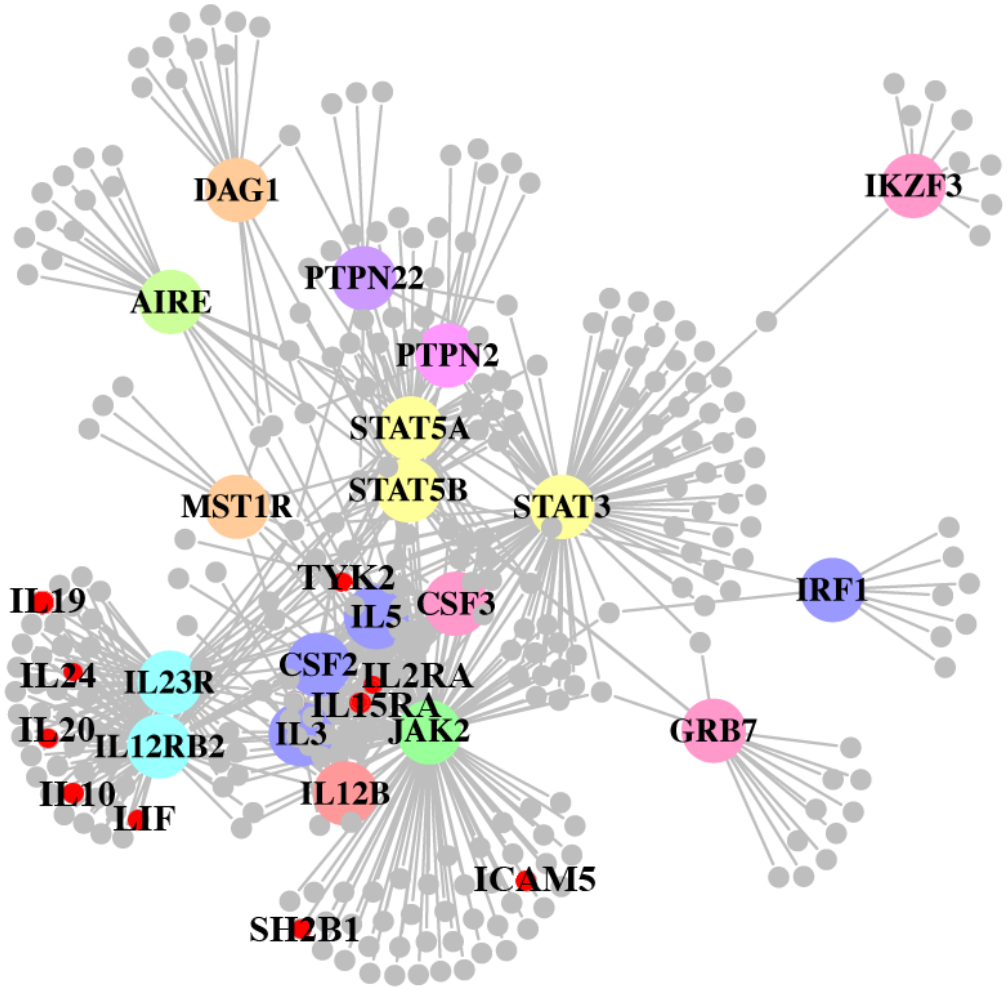
- Complement is involved

Six new treatment in pipelines

- Complement-Based Therapies

Stanford MEDICINE

Pathway Analysis of Genetic Markers



Large samples GWA on subjective sleep

- Overlapping circadian genes found through GWA and basic biology (Kalmbach et al., 2017)
- Tight relationships with neuropsychiatry:
  - Genetic architecture of Long sleep duration overlaps with that of Schizophrenia/bipolar (Lane et al. 2017)
    - This complements our finding on KLS and TRANK1
- May redefine some pathologies:
  - Insomnia shares genetic architecture with anxiety
  - Restless leg syndrome shares MEIS1 and genetic architecture with insomnia (Lane et al. 2017)

>>> Mandates studies with objective sleep