Applied Neuroscience

Computational Models of Sleep

<u>Fall 2017</u>

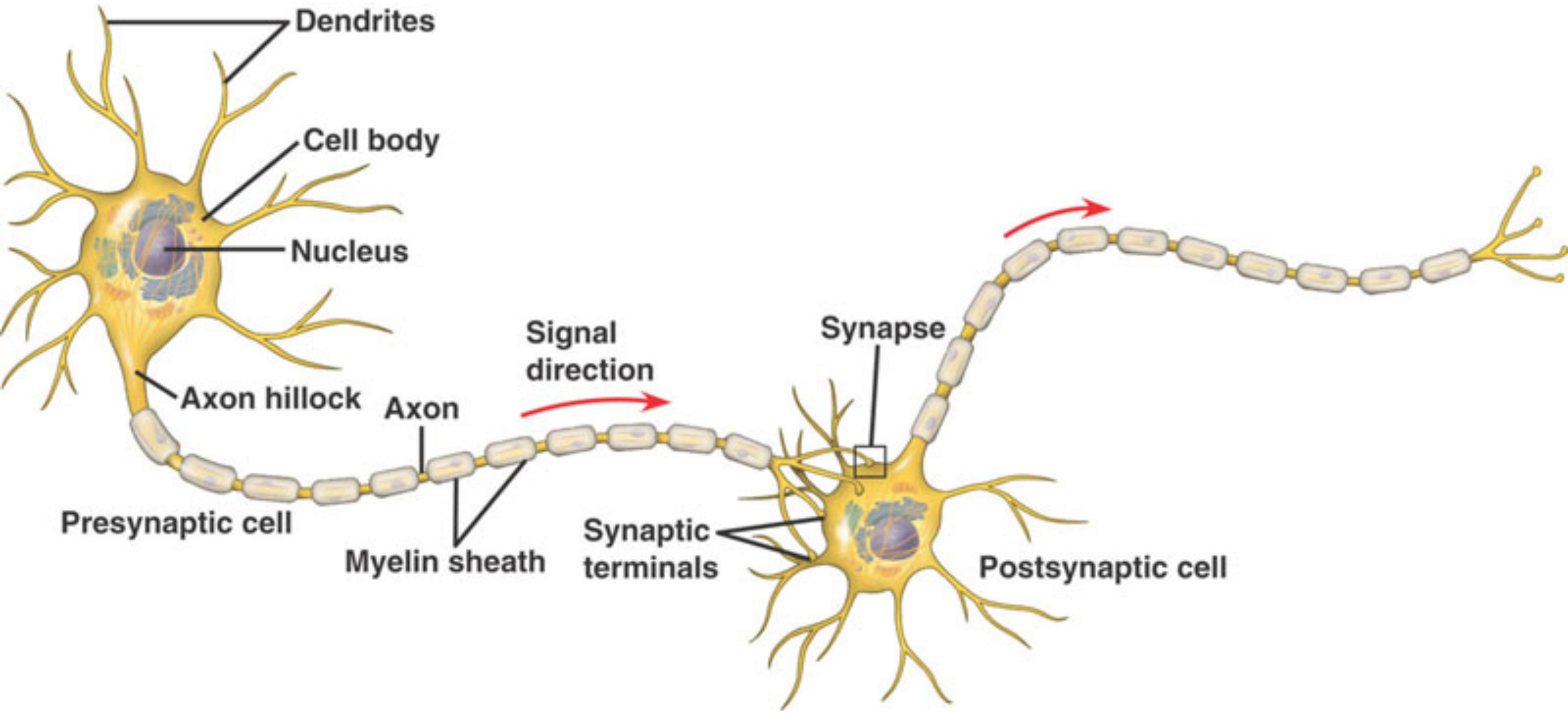
Sleep

Objective: Computational Models of Sleep

Agenda:

1. Neurobiology of Sleep
    - Action Potentials and Conduction
    - Origin of Extracellular Currents
2. Computational Models
    - Sleep Time-Frequency Spectra
    - Seizure Prediction in Epilepsy

The Neuron

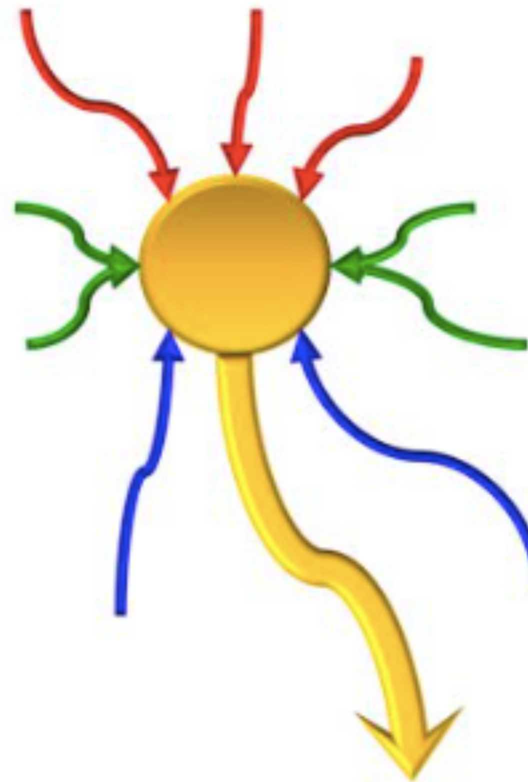


- **Axons** carry information from the **cell body** to the axon terminals
- **Axon terminals** communicate with their target cells at **synapses**

The Neuron

Signal Transmission and Interpretation

- Direction of signal transmission: neurons
  - transmit signals only in one direction (from dendrites to axon terminals), but
  - receive signals from different sources
    - Earlier or 'lower' processing stages ('bottom-up' or 'feed-forward')
    - Neighboring neurons in the same area ('lateral')
    - Subsequent or 'higher' processing areas ('top-down' or 'feedback')



- Combination of feed-forward and feed-back signal loops :
  - Information is not just passively 'forwarded',
  - **But modified by everything else going on in the brain!**

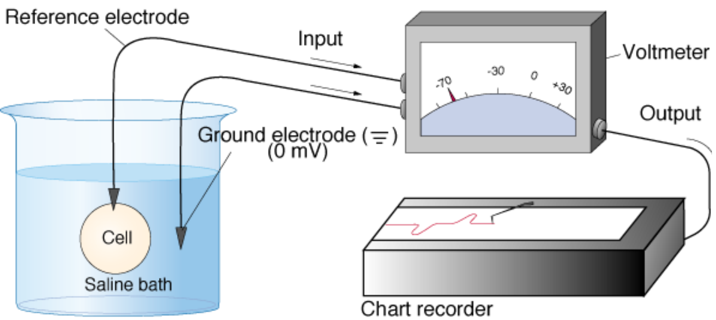
Changes in the Membrane Potential Produce Electric Signals in Nerve Cells

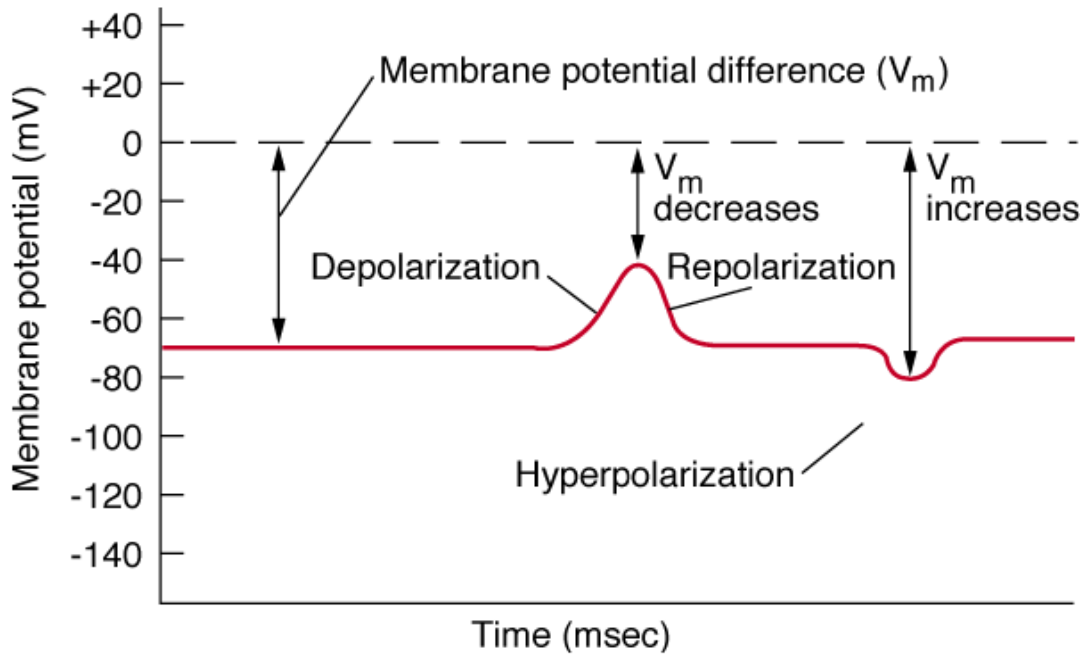
Ion	Intracellular	Extracellular	Normal Plasma Value
K^+	150	5	3.5-5.0
Na^+	12	140	135-145
Cl^-	10	105	100-108
Organic Anions	65	0	

- Difference in ion concentration between compartments gives rise to the resting membrane potential (RMP). Membrane permeability to these ions also influences the RMP.

- Transient changes from the RMP produce electrical signals which transmit information in nerve cells.

Terminology Associated with Changes in Membrane Potential





- Depolarization- a decrease in the potential difference between the inside and outside of the cell.
- Hyperpolarization- an increase in the potential difference between the inside and outside of the cell.
- Repolarization- returning to the RMP from either direction.
- Overshoot- when the inside of the cell becomes +ve due to the reversal of the membrane potential polarity.

Gated Channels Are Involved in Neuronal Signaling

In the nervous system, different channel types are responsible for transmitting electrical signals over long and short distances:

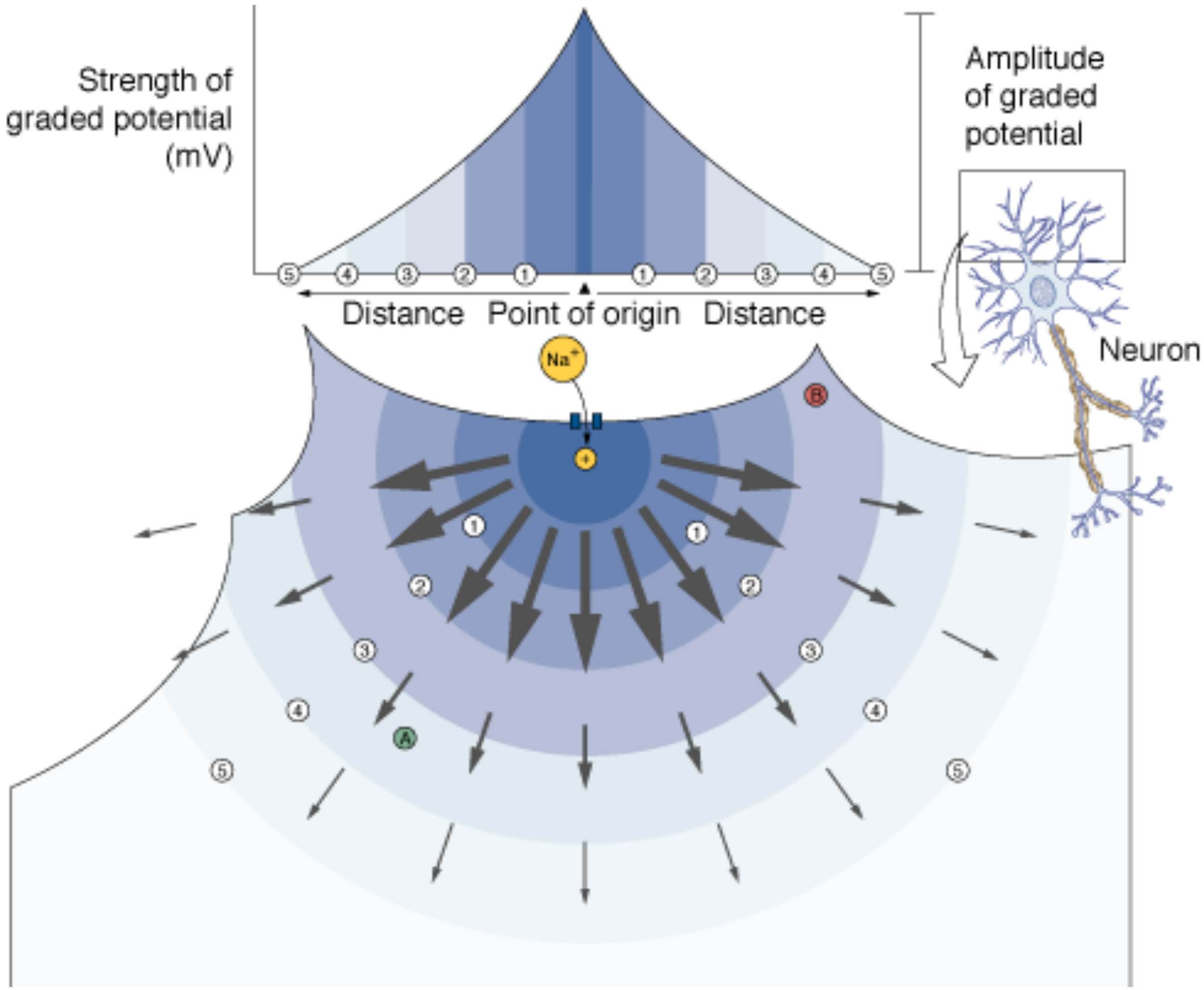
A. Graded potentials travel over short distances and are activated by the opening of mechanically or chemically gated channels.

B. Action potentials travel over long distances and they are generated by the opening of voltage-gated channels.

Gated ion channels in the membrane open to a variety of stimuli:

- Mechanical force, eg. sensory neurons.
- Chemical ligands, eg. neurotransmitters.
- Voltage, eg. changes in the resting membrane potential.

Graded Potentials

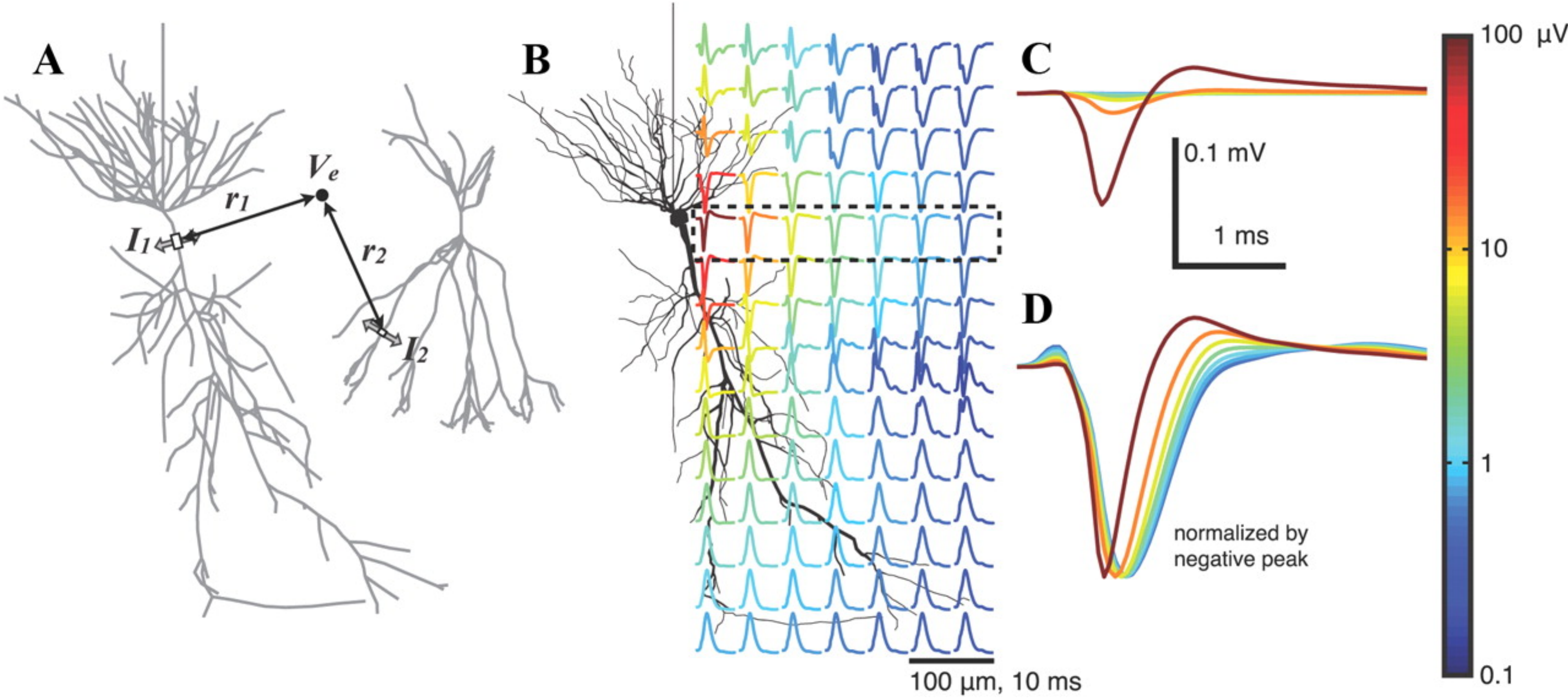


F8-9

•<u>Graded potentials</u> are depolarizations or hyperpolarizations whose strength is proportional to the strength of the triggering event.

•Graded potentials lose their strength as they move through the cell due to the leakage of charge across the membrane (eg. leaky water hose).

Average extracellular action potential (EAP) of the pyramidal cell model.



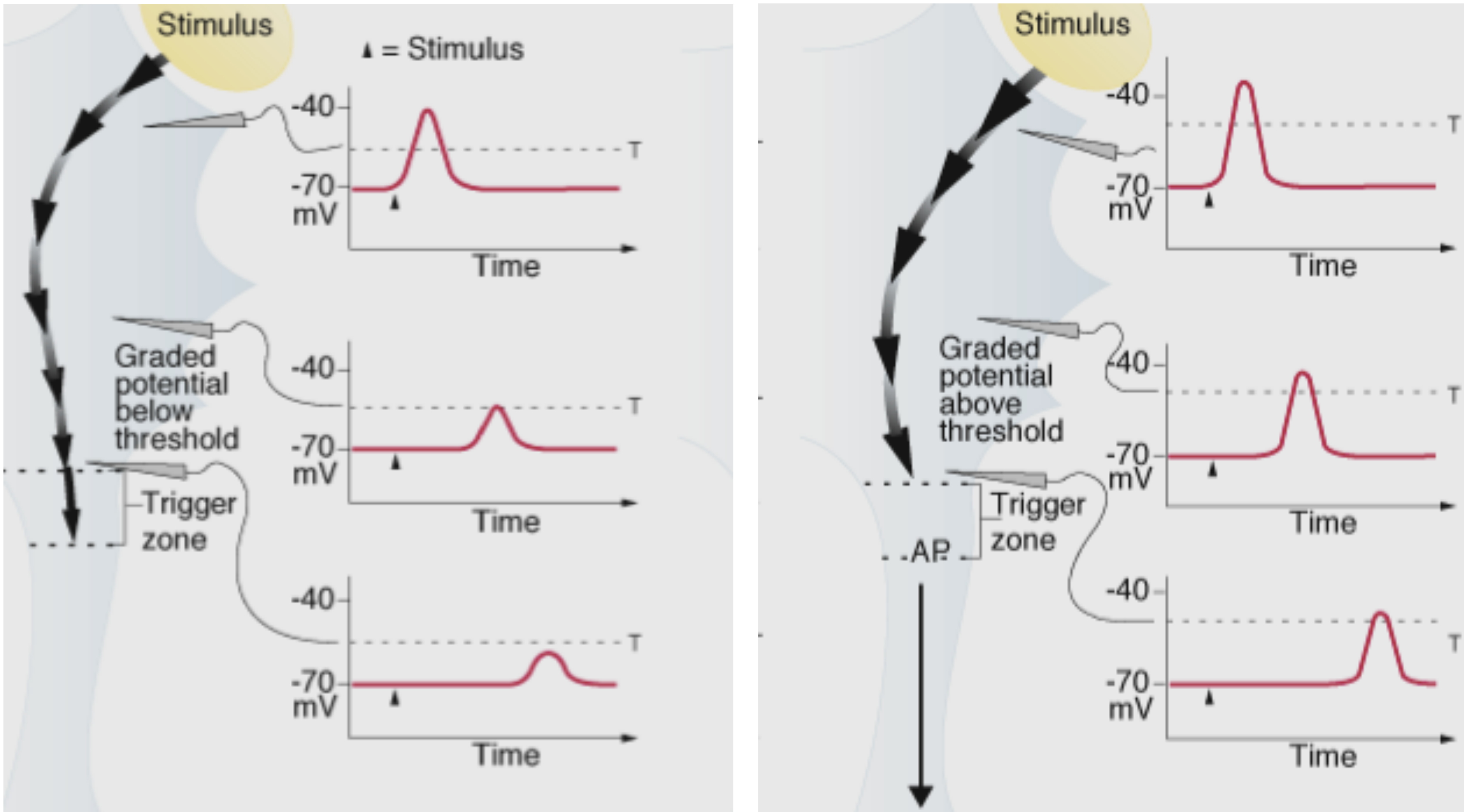
Erik W. Schomburg et al. J. Neurosci. 2012;32:11798-11811

The Journal of Neuroscience

Graded Potentials

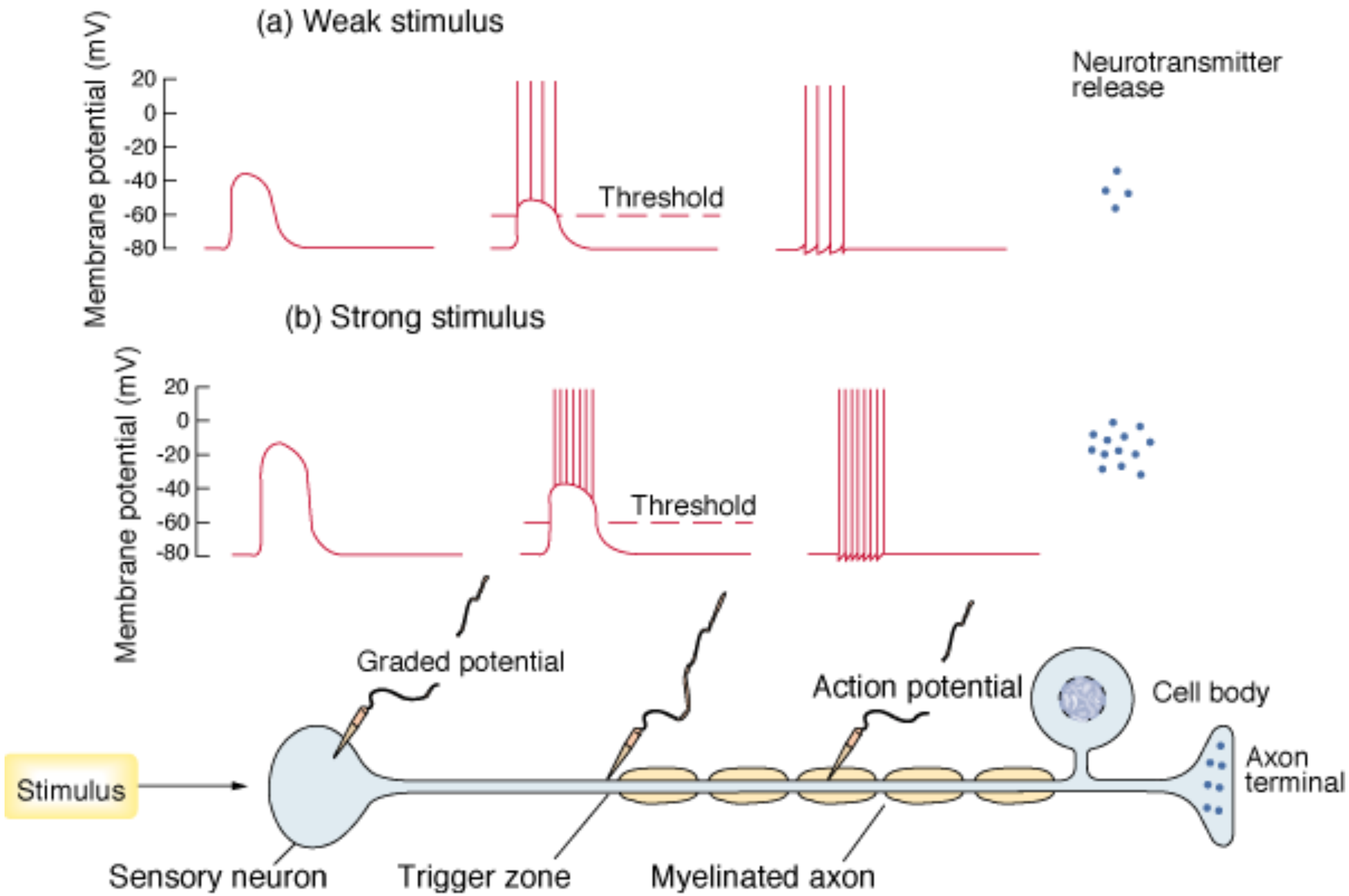
- A graded potential depolarization is called excitatory postsynaptic potential (EPSP). A graded potential hyperpolarization is called an inhibitory postsynaptic potentials (IPSP).
- They occur in the cell body and dendrites of the neuron.
- The wave of depolarization or hyperpolarization which moves through the cell with a graded potential is known as local current flow.

Graded Potentials Above Threshold Voltage Trigger Action Potentials



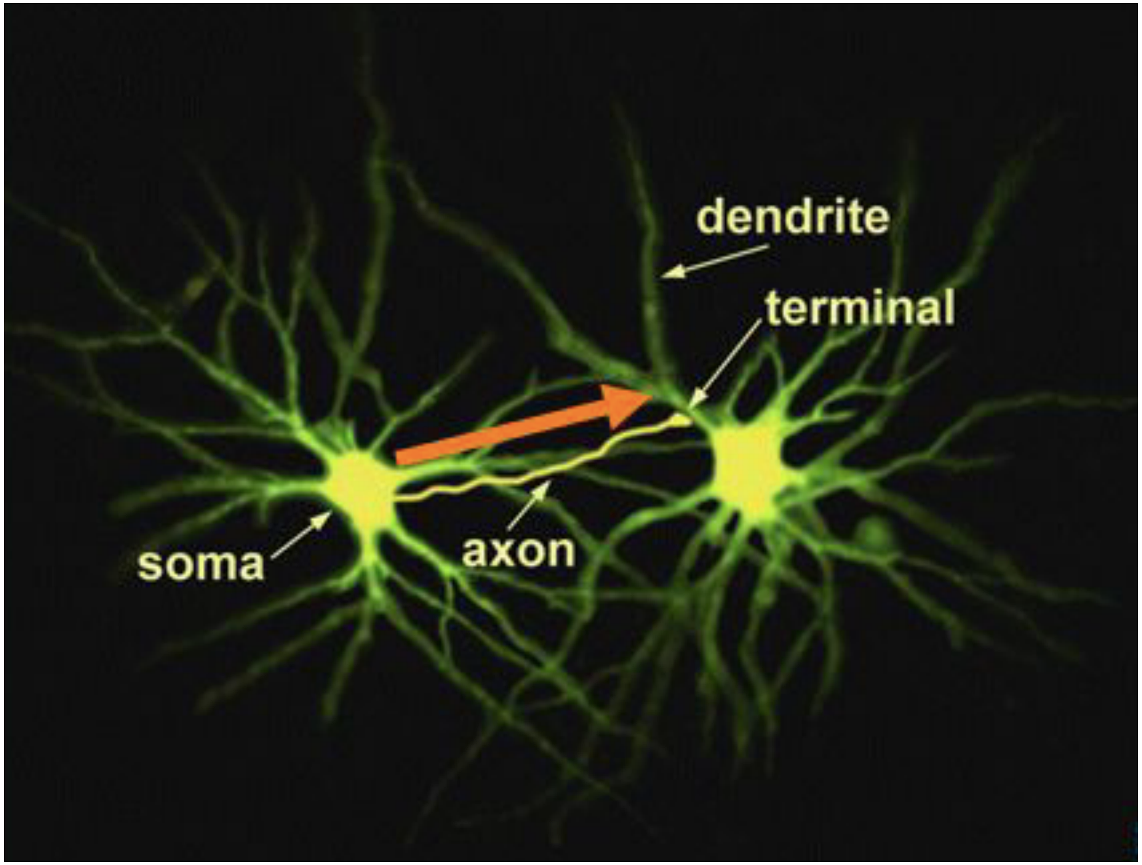
Graded potentials travel through the neuron until they reach the trigger zone. If they depolarize the membrane above threshold voltage (about -55 mV in mammals), an action potential is triggered and it travels down the axon.

Frequency of Action Potential Firing is Proportional to the Size of the Graded Potential



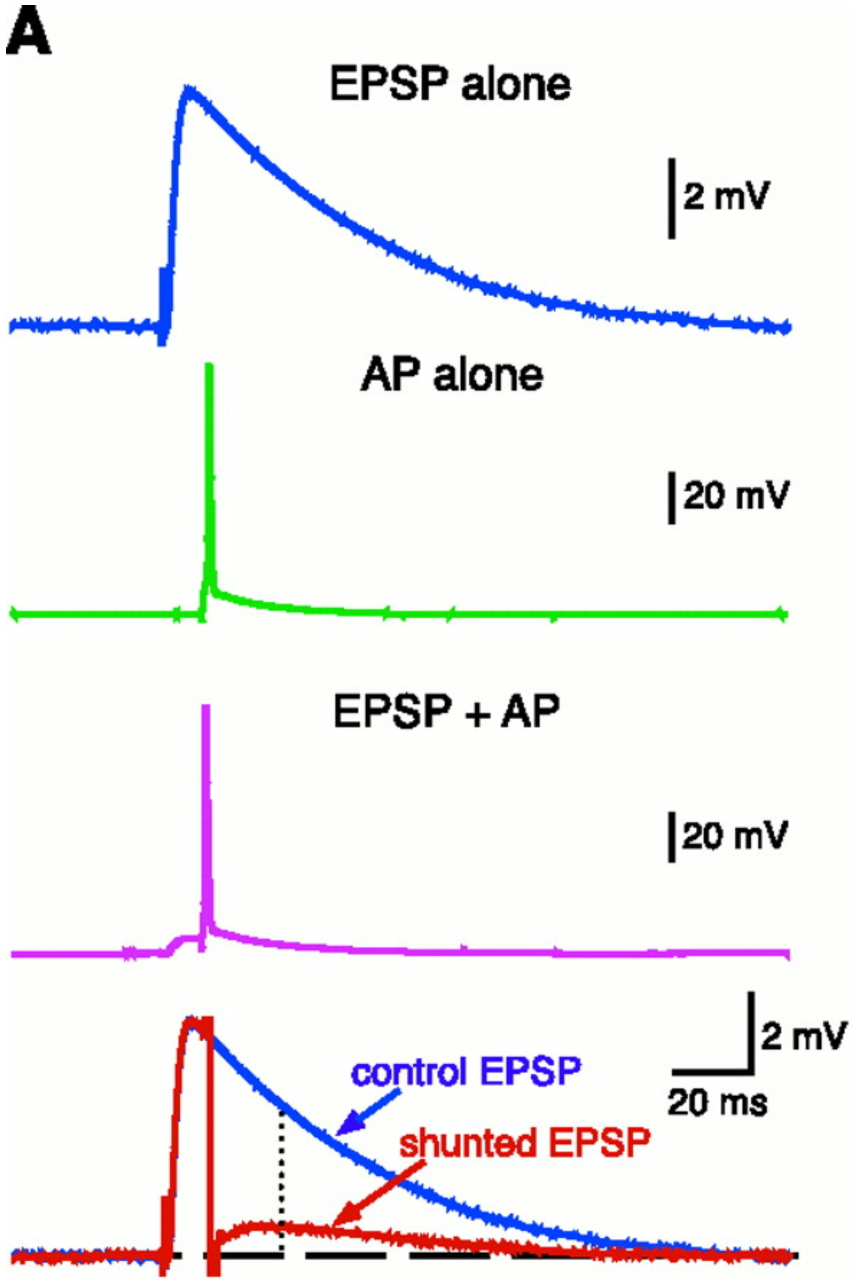
The amount of neurotransmitter released from the axon terminal is proportional to the frequency of action potentials.

Neural Transmission



- Neurons receive input from other neurons, especially through their dendrites
- Neurons send output in the form of an action potential (AP) along their axons
- When an AP arrives at the synaptic end bulb of a pre-synaptic neuron, neurotransmitter (NT) is released
- NTs bind to receptors on the post-synaptic neuron, which often opens ion channels
- The flow of ions causes an electrical current in the membrane
- These graded potentials can be either
  - Positive/Depolarization/ Excitatory
  - Negative/ Hyperpolarization/ Inhibitory
- The graded potentials are summed in the axon hillock
- If the sum exceeds threshold, then the post-synaptic neuron will fire an action potential
- When the action potential reaches the synaptic end bulb, NTs are released, and the cycle begins again

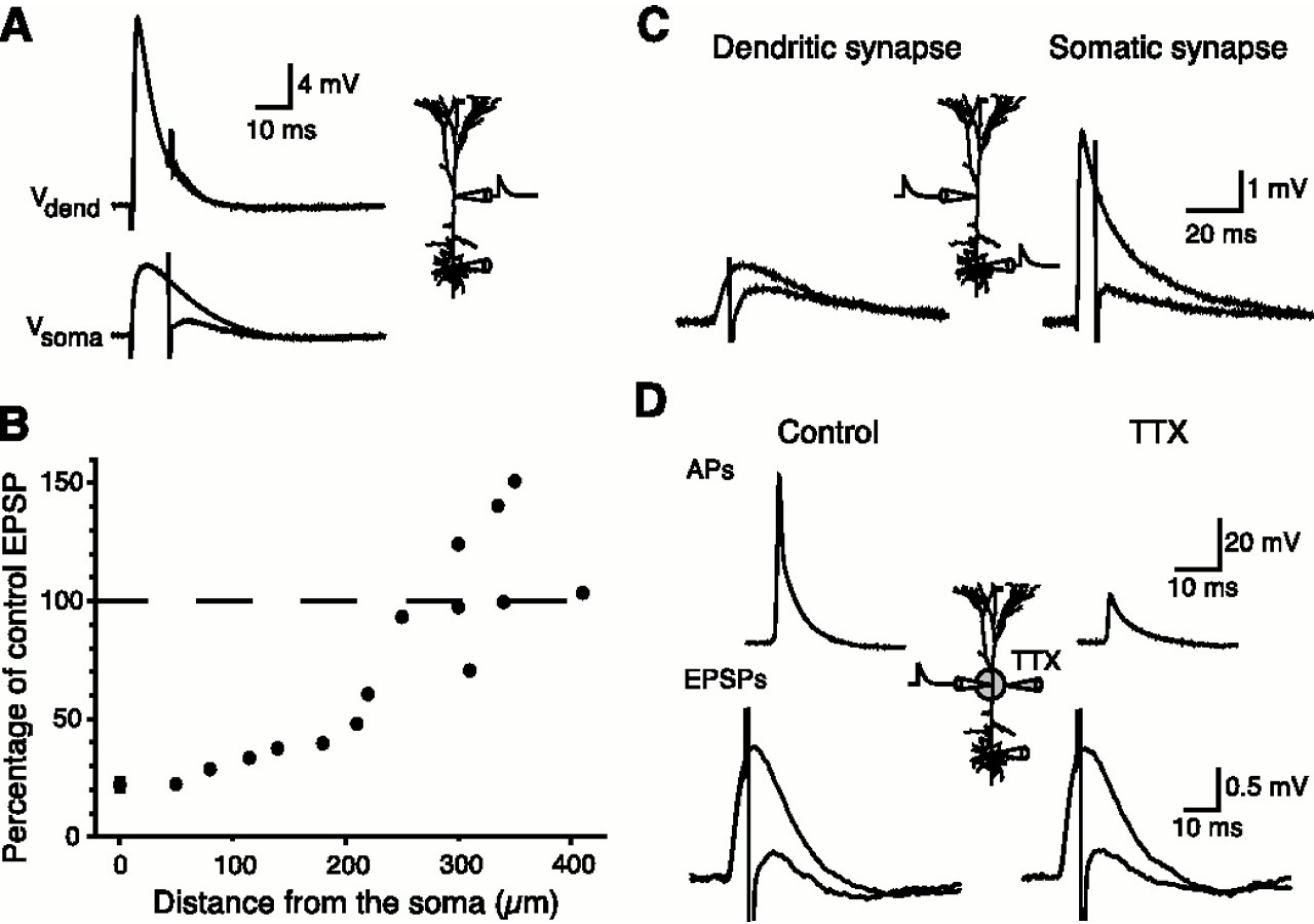
EPSPs and Action Potentials



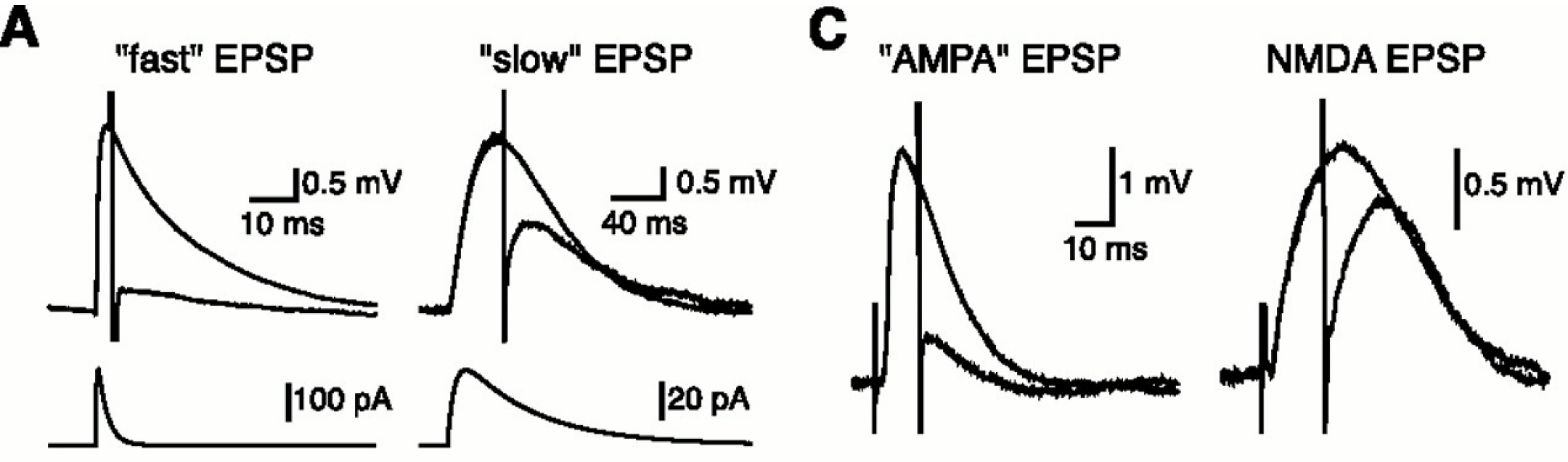
Source: Hausser et al, Science Vol. 291. 138-141

Neurons encode information and communicate via action potentials, which are generated by the summation of synaptic events.

It was previously thought that APs reset the membrane potential completely.
However, the strength of this reset is variable.
EPSPs shunt, or diminish, the AP response in pyramidal neurons.


A
4 mV
10 ms
V_{dend}
V_{soma}
B
Percentage of control EPSP
150
100
50
0
0
100
200
300
400
Distance from the soma (μm)
C
Dendritic synapse
Somatic synapse
1 mV
20 ms
D
Control
TTX
APs
20 mV
10 ms
TTX
EPSPs
0.5 mV
10 ms

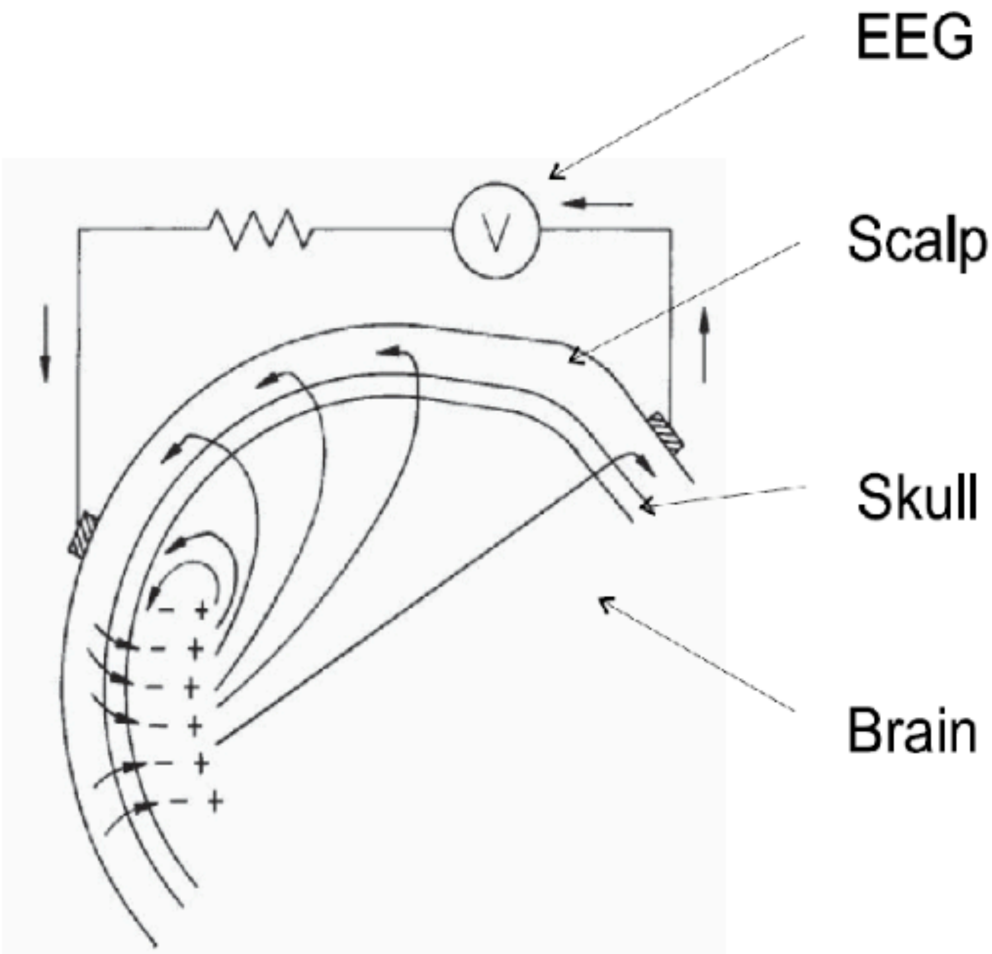
EPSPs and Action Potentials



Source: Hausser et al, Science Vol. 291. 138-141

EPSP shunting depends on synaptic input kinetics. The rise and decay times differ between “fast” and “slow” EPSPs.

Electroenchaplography (EEG)

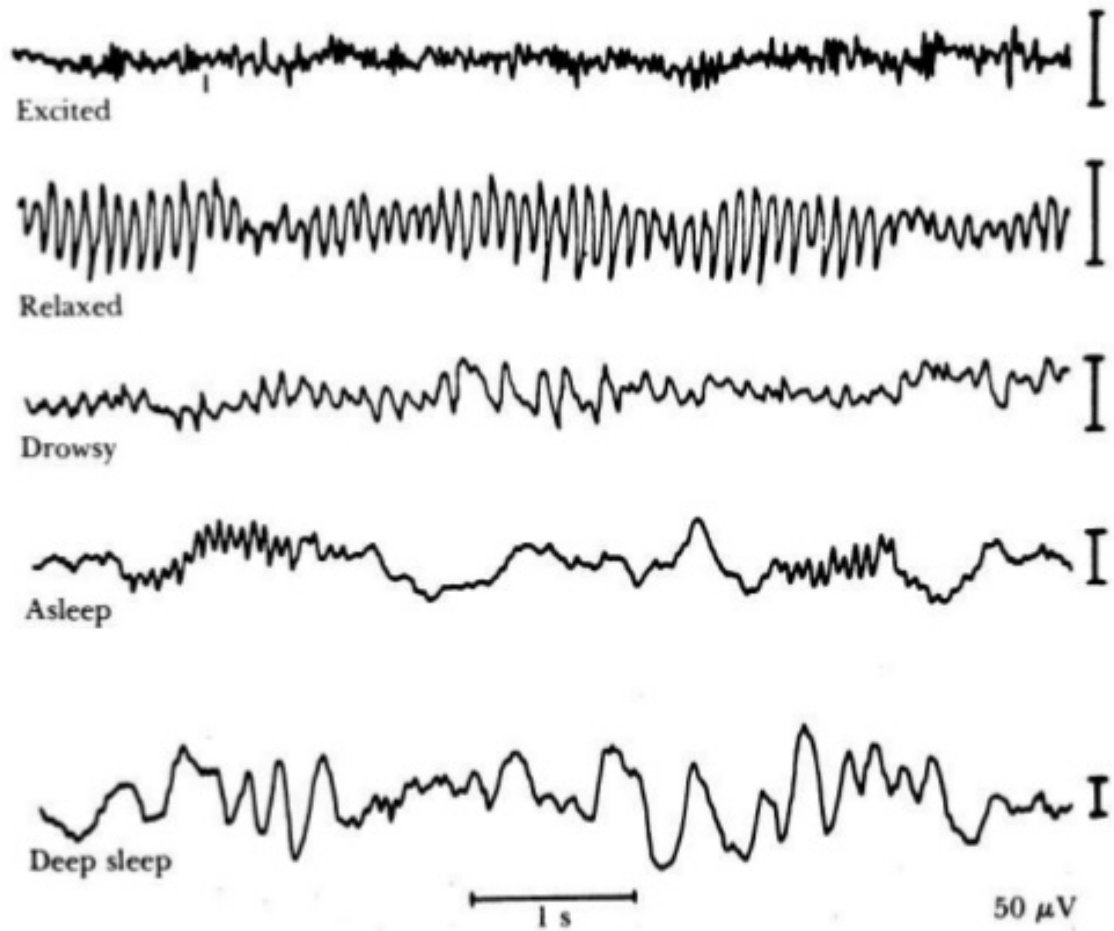


Current in the EEG measuring circuit depends on the nature and location of the current sources, on the electrical properties of the brain, skull and scalp and on location of both electrodes. *Source: Nunez et al (1891)*

Electroenchaplography (EEG)

EEG is an electrophysiological monitoring method to record electrical activity of the brain:

- Often non-invasive
- Measures voltage fluctuations resulting from ionic current within neurons
- Used to diagnose epilepsy
- Limited spatial resolution
- Temporal resolution at millisecond scale



Test Your Understanding:

EEG activity is thought to arise from which of the following?

A. Cortical layers I and VI
B. Axonal action potentials
C. Horizontal dipoles
D. Excitatory and inhibitory post-synaptic potentials

Test Your Understanding:

EEG activity is thought to arise from which of the following?

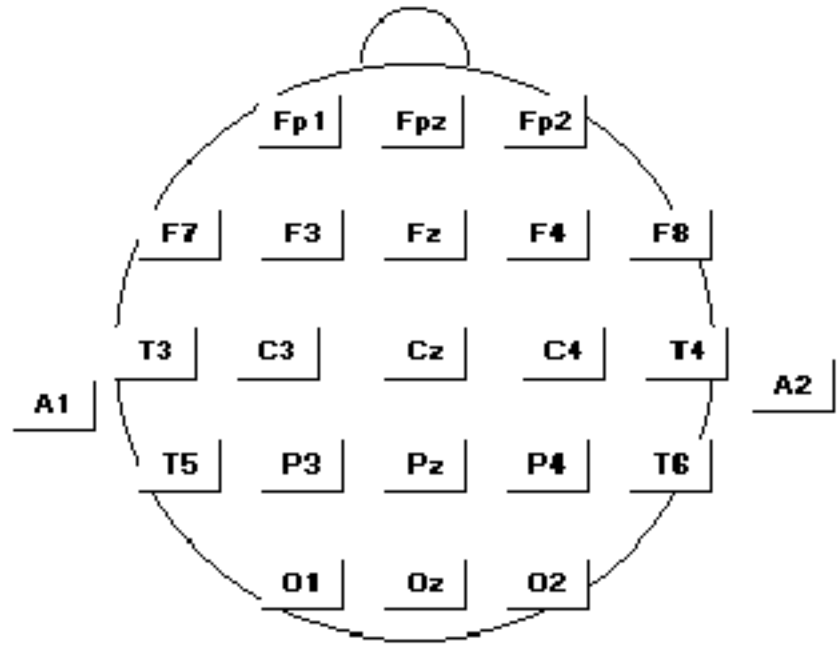
A. Cortical layers I and VI
B. Axonal action potentials
C. Horizontal dipoles
D. Excitatory and inhibitory post-synaptic potentials

Explanation: EEG activity arises from the outermost cortex layer I and does not directly capture axonal action potentials. EEG is most sensitive to post-synaptic potentials generated in the superficial layers of the cortex.

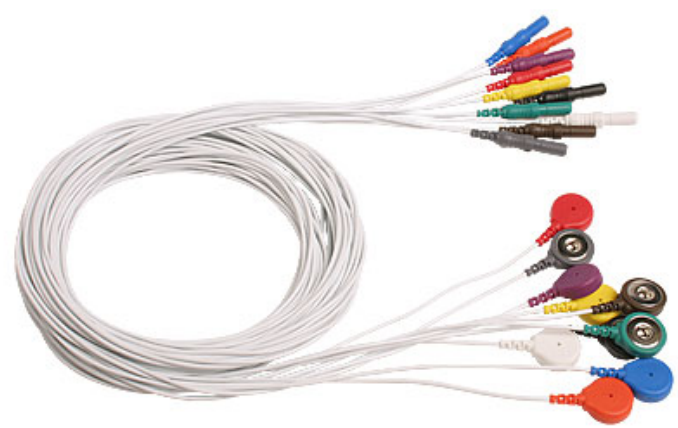
Electrodes

Electrodes are small metal discs that are places on the scalp in special positions.

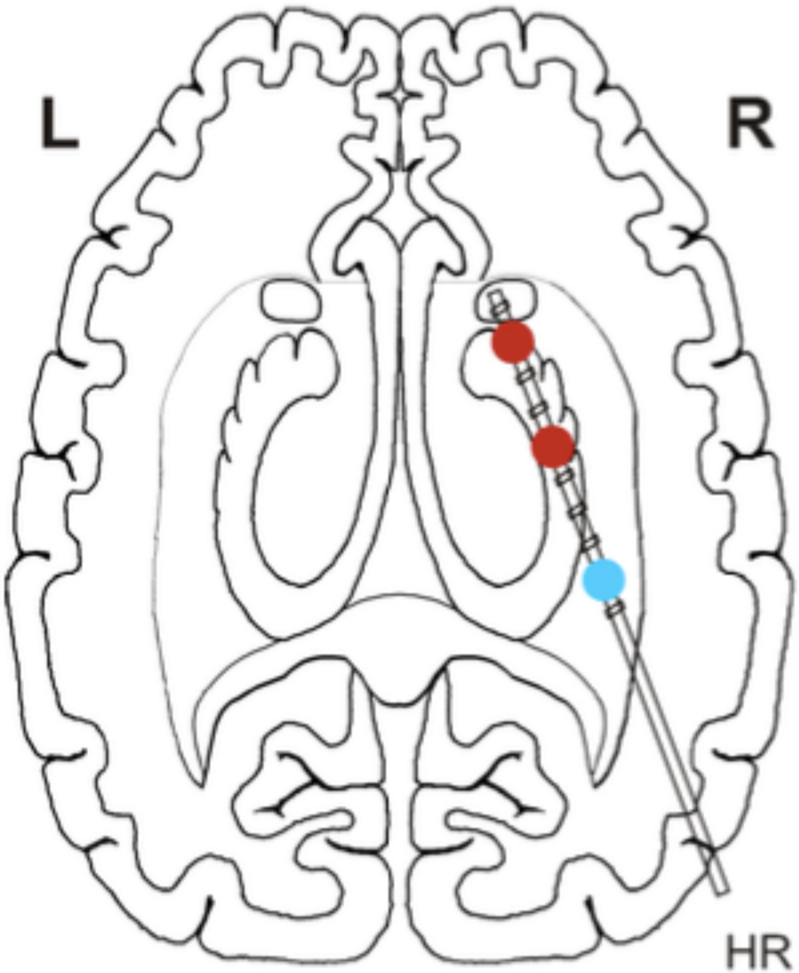
- Each electrode site is labeled with a letter and a number
- Letter: F is frontal lobe and T is temporal lobe
- Number: Even number means right side of head and odd number means left side of head
- Can be made of: stainless steel, tin, gold or silver covered with a silver chloride coating



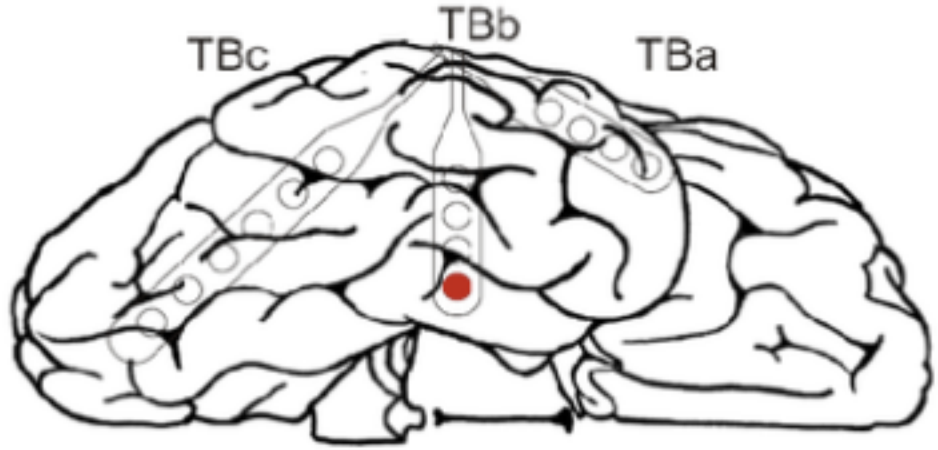
10/20 System of electrode placement



Intra(cranial/cerebral) EEG



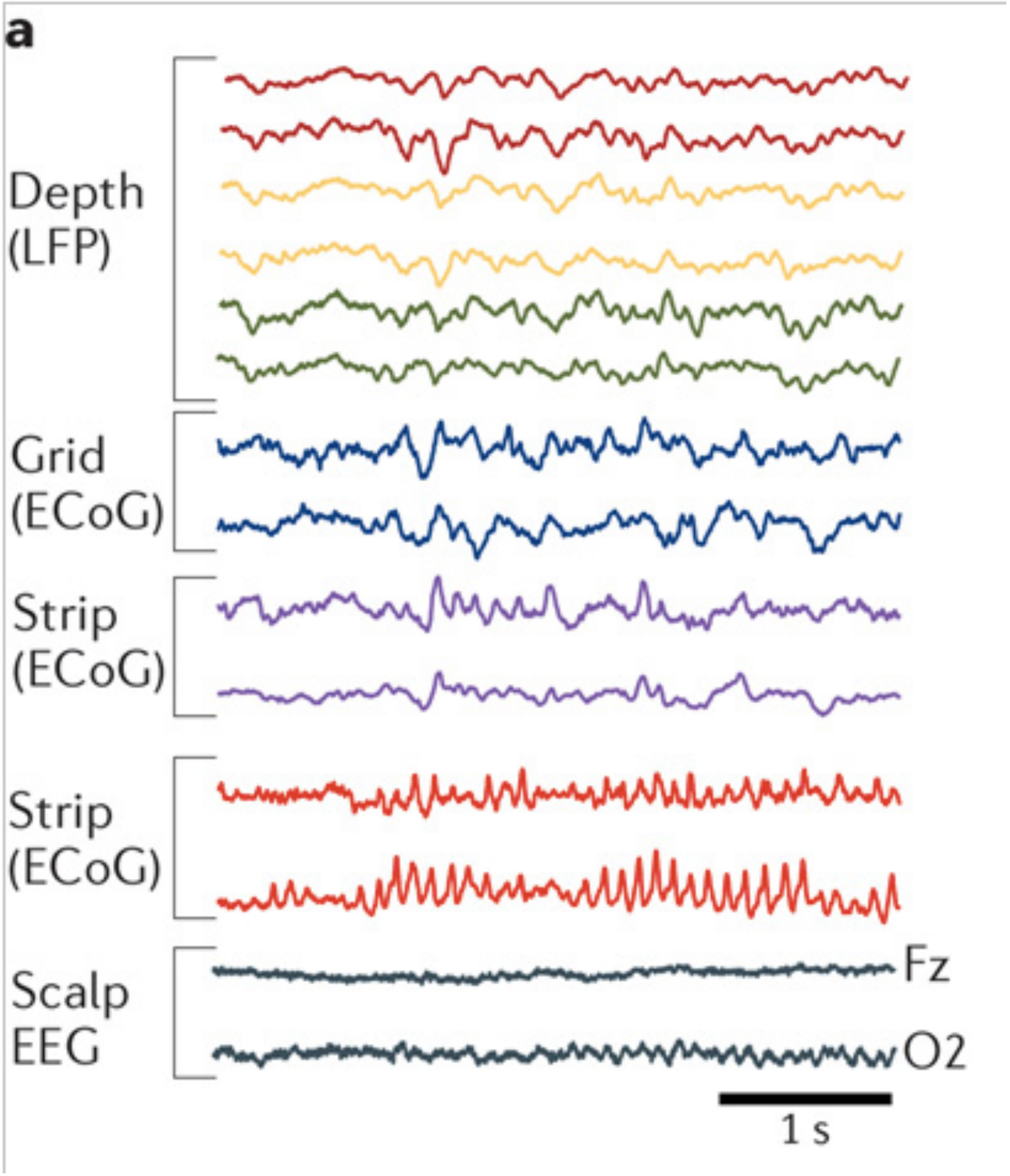
Depth electrodes



Strip electrodes

Grid electrodes

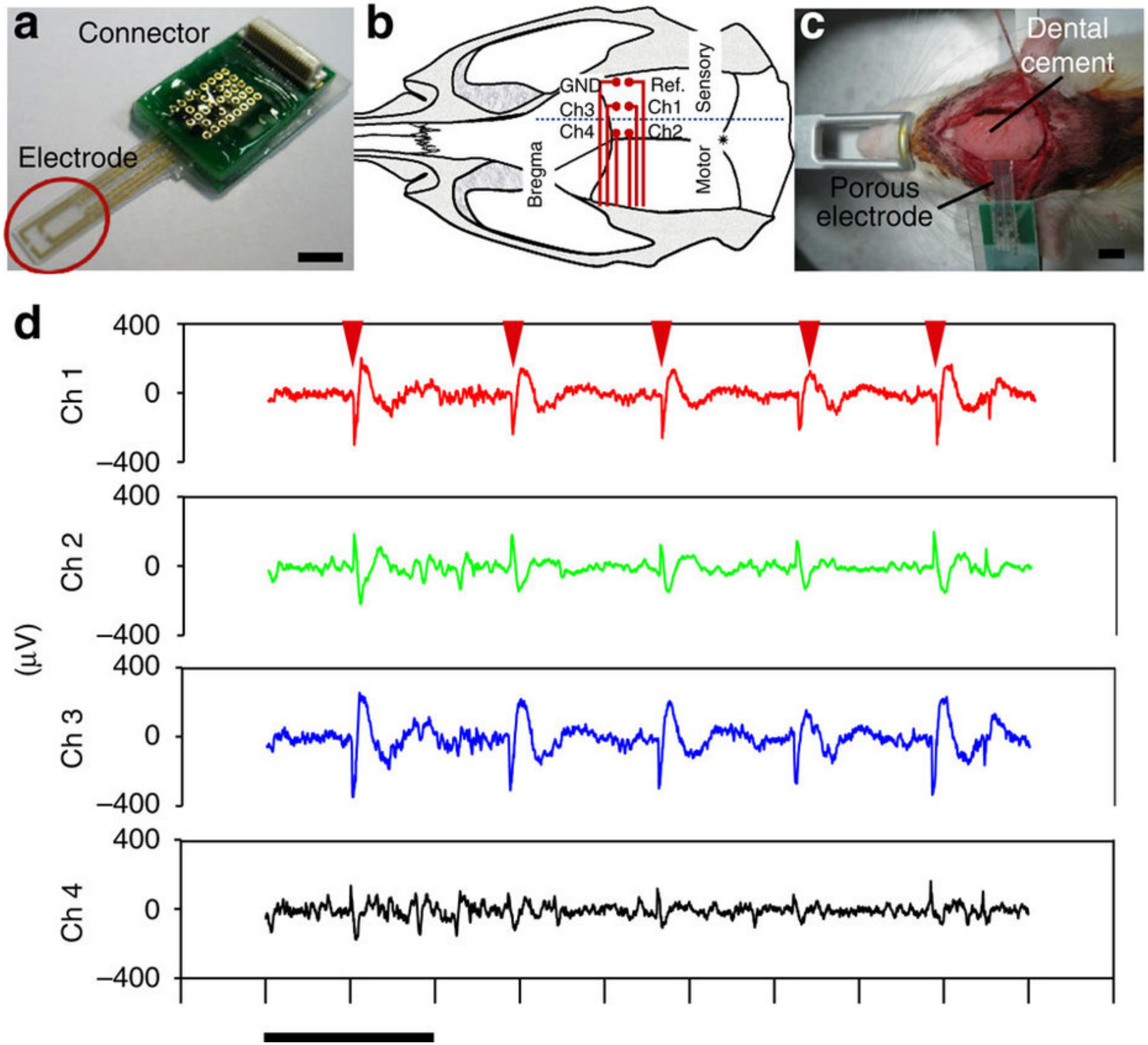
Recording Methods of Extracellular Events



Local field potential (LFP):

- Micro-EEG
- Records deep brain activity while EEG, MEG and ECoG mainly sample electrical activity that occurs in the superficial layers of the cortex
- Electrodes can be made of silicon, metal or glass
- Spiking activity of a large neural population in a small volume can be monitored with a large density of recording sites

EEG Monitoring



a. Electrode used to measure evoked potential signal from the skull of a rat

b. Location of electrode array

c. Electrode mounted and fixed with dental cement

d. Electrode recordings of voltage over time

Recording Methods of Extracellular Events

Electroencephalography (EEG):

- Spatio-temporally smoothed version of the local field potential (LFP), integrated over a larger area
- Used in combination with structural MRI imaging

Magnetoencephalography (MEG):

- Measures tiny magnetic fields outside that skull from currents generated by the neurons
- Non-invasive
- High spatio-temporal resolution

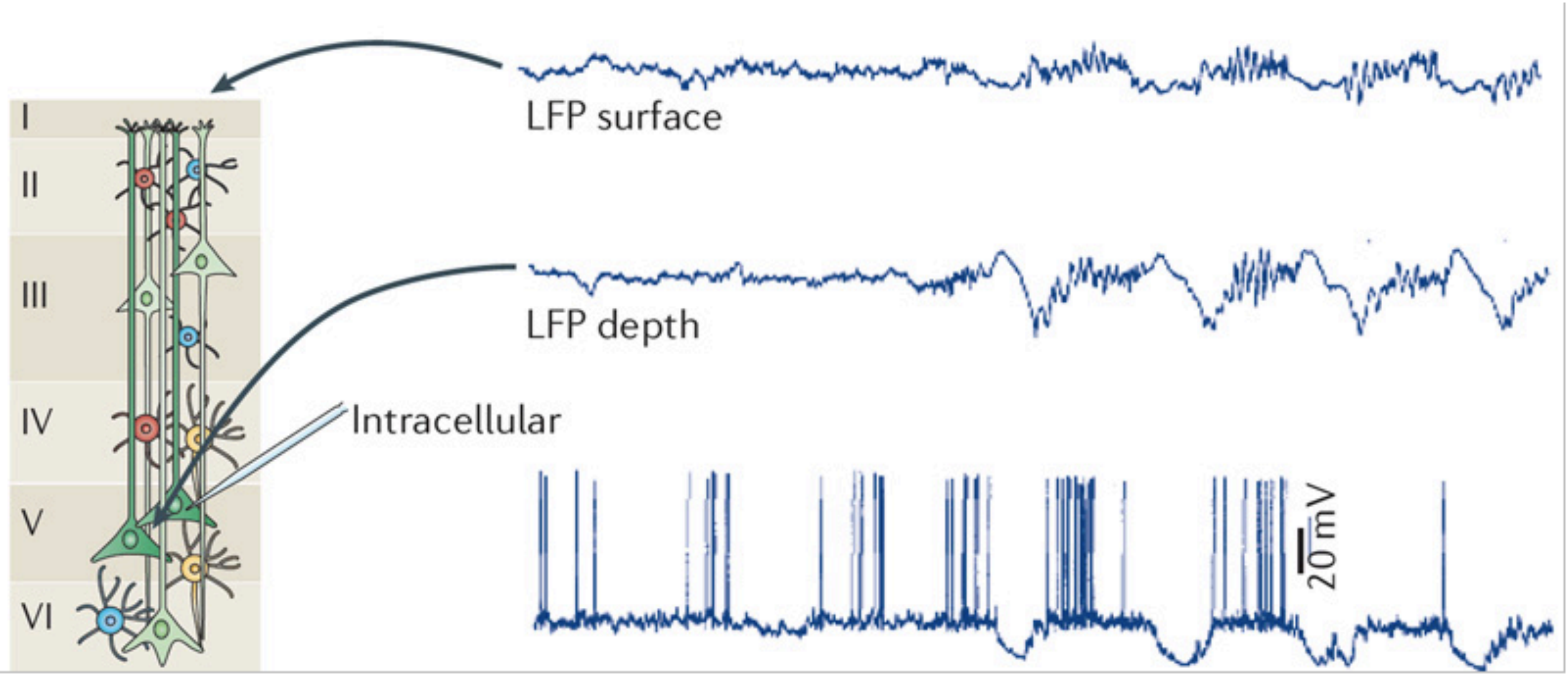
Electrocorticography (ECoG):

- Uses subdural platinum-iridium or stainless steel electrodes to record electric activity directly from the surface of the cerebral cortex, thereby bypassing signal-distorting skull and intermediate tissue

Voltage-sensitive dye imaging:

- Membrane voltage of neurons can be detected optically with voltage-sensitive proteins

Recording Methods of Extracellular Events



Simultaneously recorded LFP traces from the superficial ('surface') and deep ('depth') layers of the motor cortex in an anaesthetized cat and an intracellular trace from a layer 5 pyramidal neuron. Note the alternation of hyperpolarization and depolarization (slow oscillation) of the layer 5 neuron and the corresponding changes in the LFP. The positive waves in the deep layer (close to the recorded neuron) are also known as delta waves. iEEG, intracranial EEG.

Computational Models of Sleep

Prominent Computational Neuroscientists:
Gyorgy Buzsaki, NYU
Terry Sejnowski, UCSD
Roger Traub, IBM

What is the biological function of sleep?
Why do we dream?
What are the underlying brain mechanisms?
What is its relation to anesthesia?

Sleep

Sleep is divided into stages

- Apply to adults and children
- But proportion in those stages differs

How do we know?

Scientists have used sleep EEG

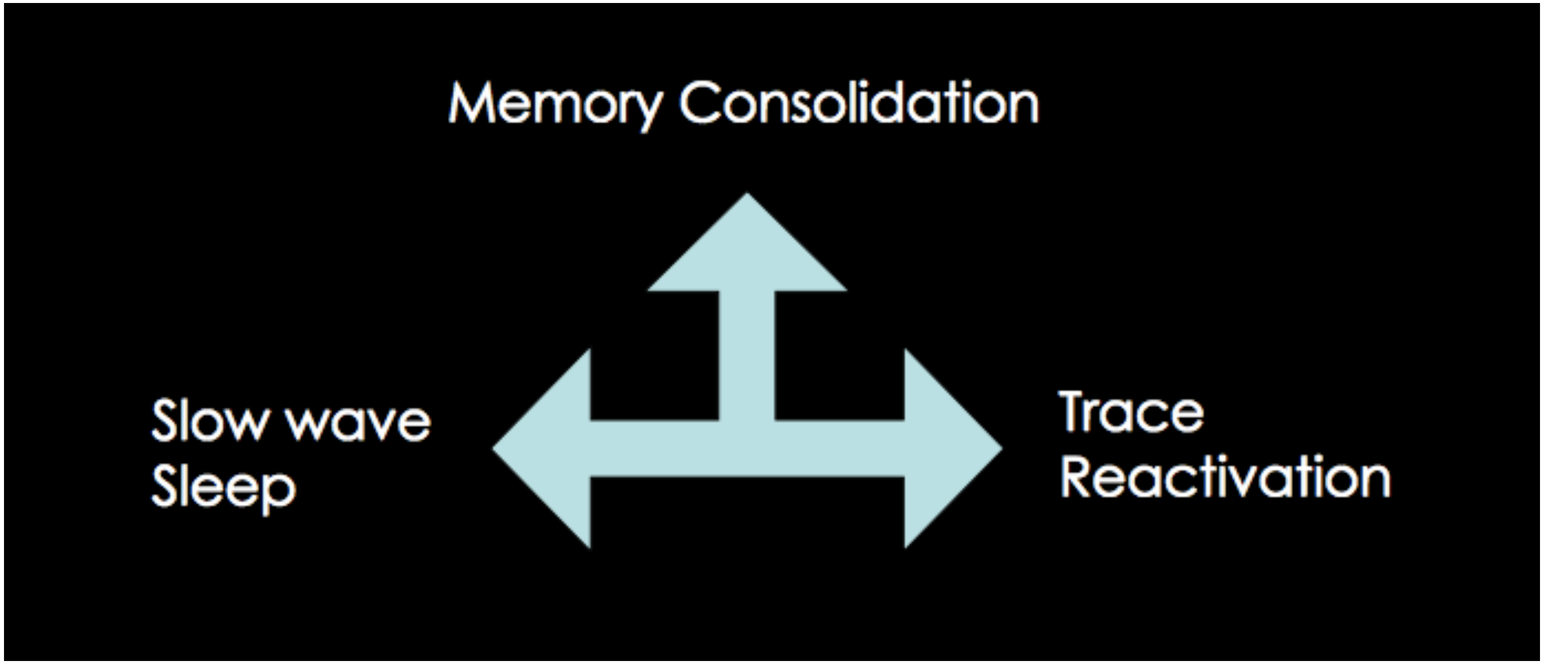
Sleep EEG measures miniscule electrical activity

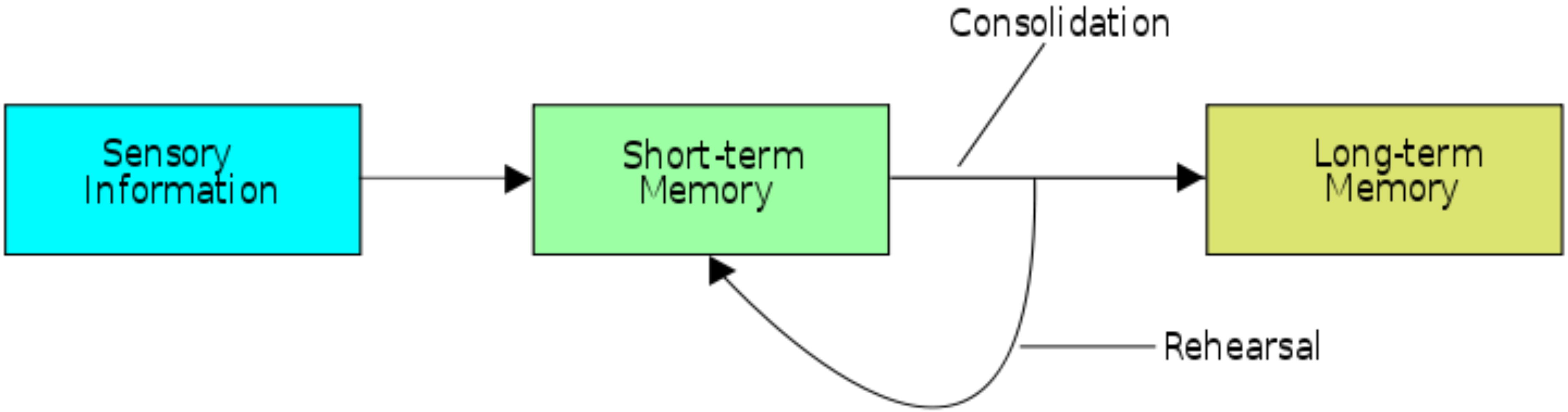
- Small electrodes placed on head
- Sensitive recording equipment determines output

Sleep EEG sometimes used in children

- To detect more troublesome sleep problems

Sleep and Memory Formation





Sleep and Memory Formation

Memory Consolidation

At the time of encoding,
memories are susceptible to disruption.
With time, they become robust to interference
(Mueller and Pilzecker, 1900)

Cerebral trauma leads to a greater loss
of recent than remote memories
(Ribot, 1882)

SLEEP

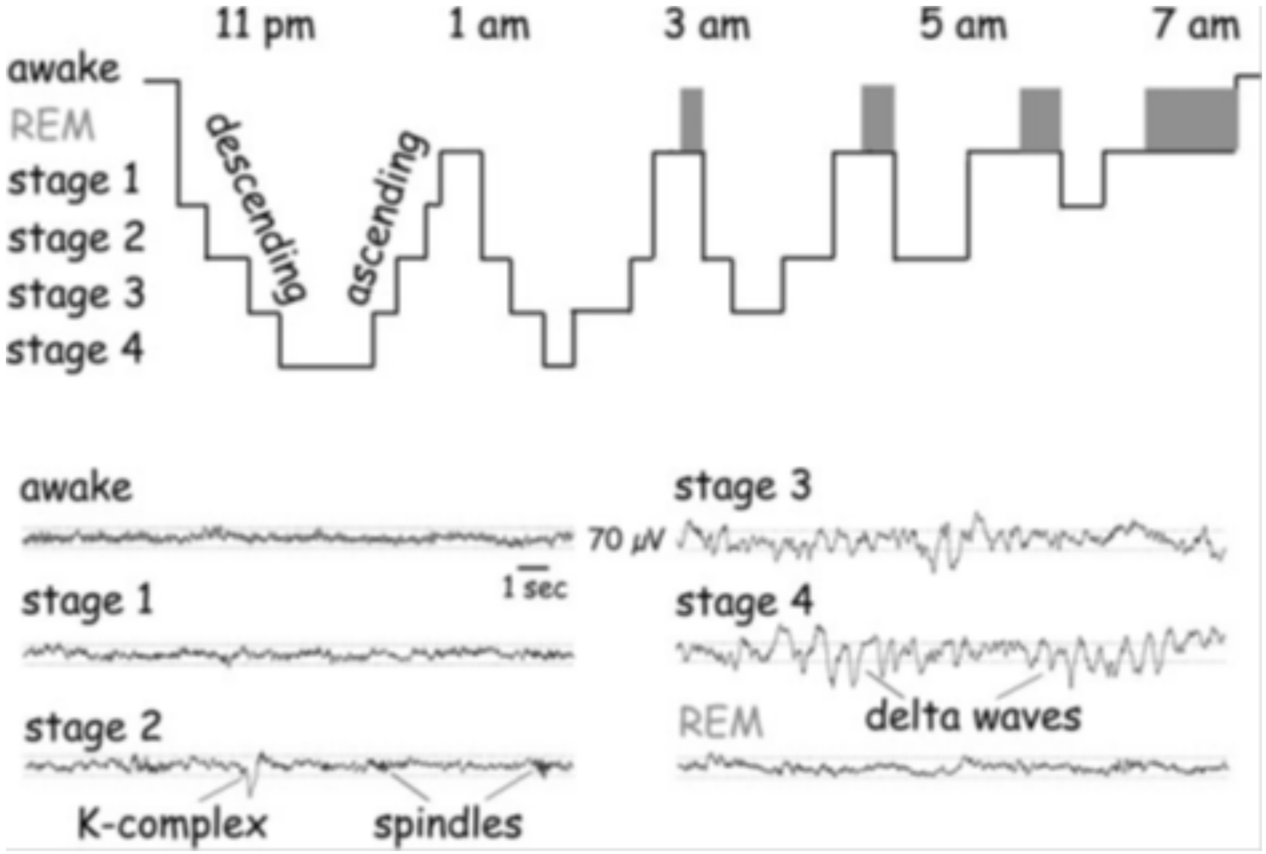
Non-REM **REM**

Stages

1 **2** **3** **4**

Spindles Slow wave,delta

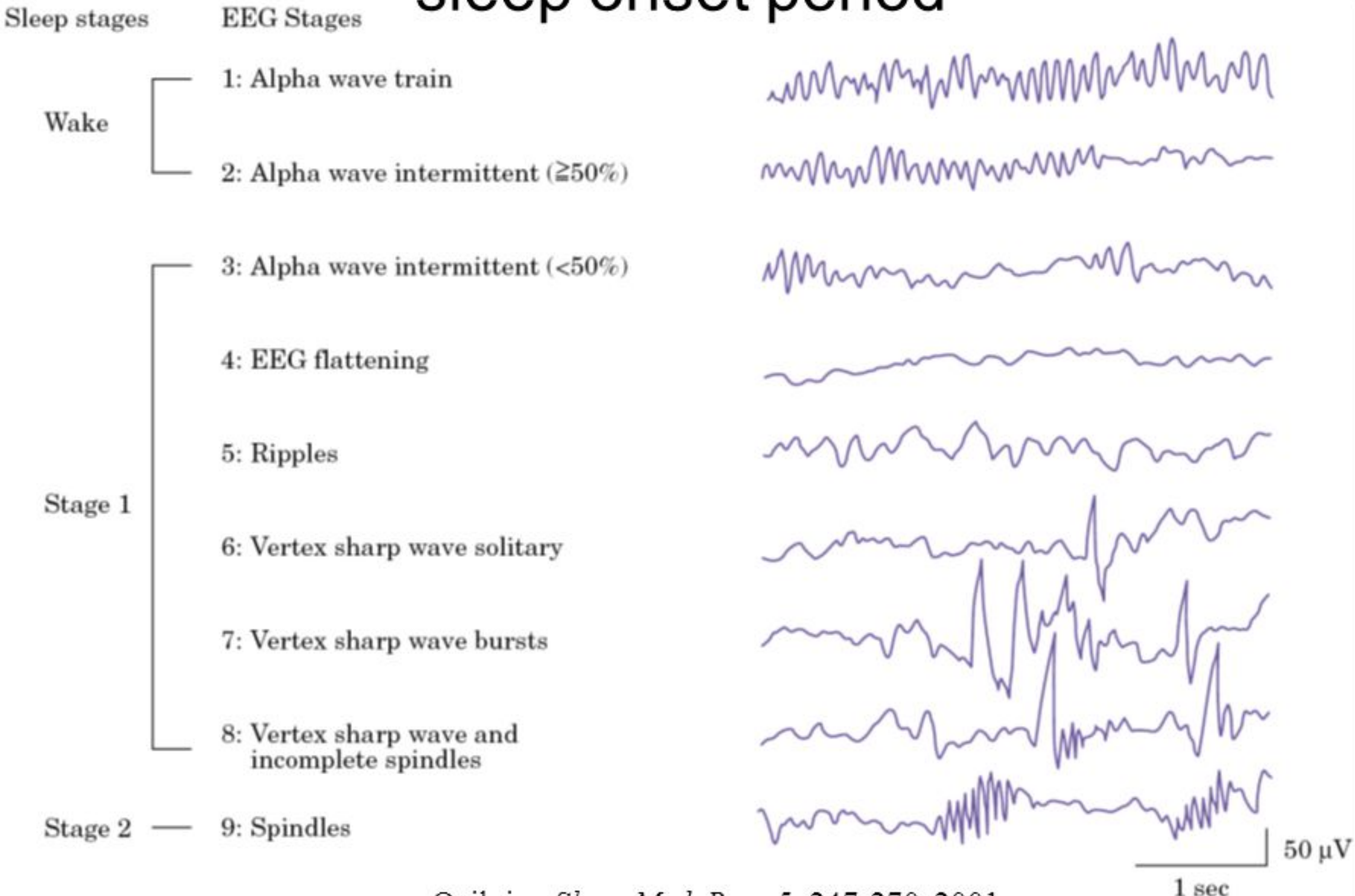
Sleep and Memory Formation



Brain rhythms

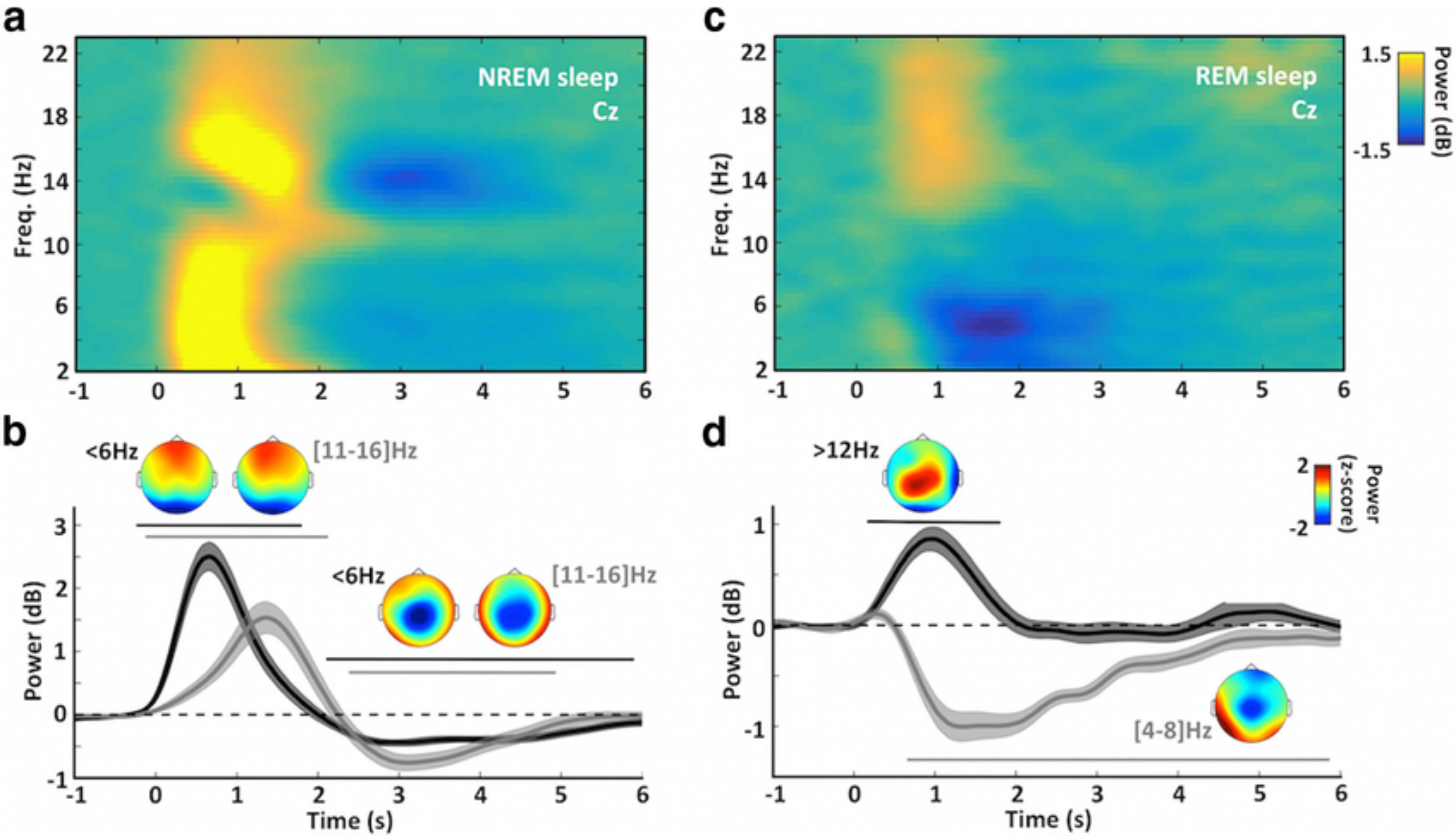
- **Alpha rhythm** (8-13 Hz) appears at the occipital cortex when eyes close. [resting condition] {rolandic mu rhythm; temporal tau rhythm}
- **Beta rhythm** (13-30 Hz) is associated with alertness.
- **Gamma rhythm** (30-80 Hz) is related to sensory integration and feature binding.
- **Theta rhythm** (4-8 or 4-10 Hz)
- **Delta rhythm** (0.5-4 or 1-4 Hz)
- **Sleep spindle** (12-15 Hz or 7-15 Hz) {sigma rhythm}
- **K complex** (<0.5 Hz) {(very) slow oscillation}

Successive EEG changes throughout the sleep onset period

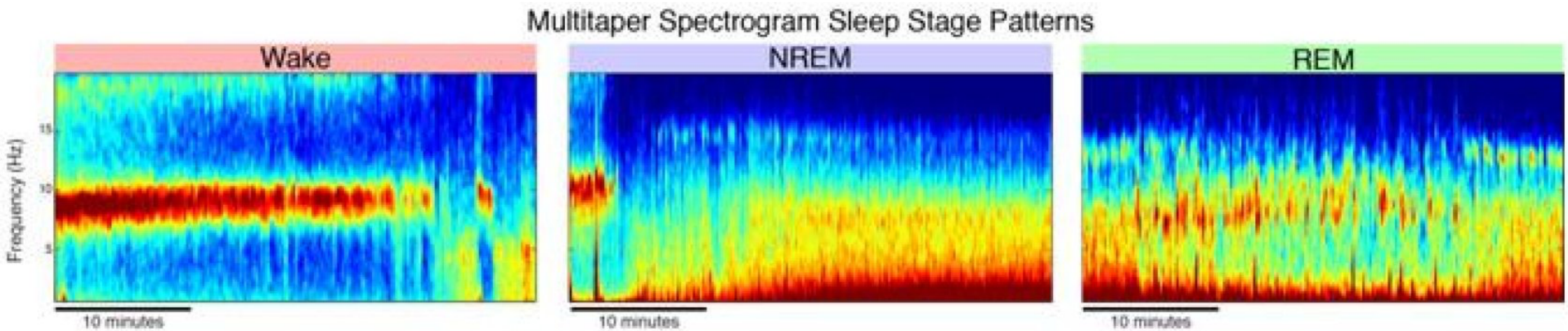


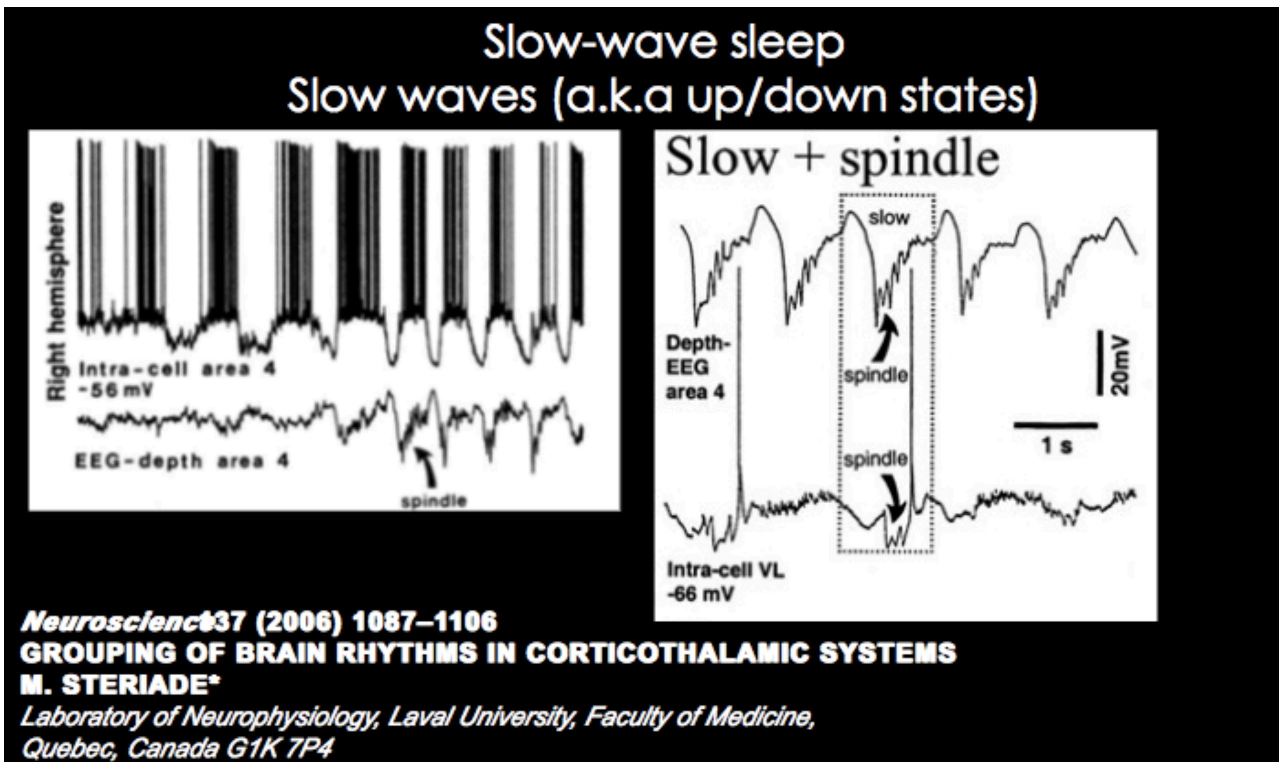
Ogilvie, *Sleep Med. Rev.*, 5, 247-270, 2001.

Sleep and Memory Formation



Sleep and Memory Formation





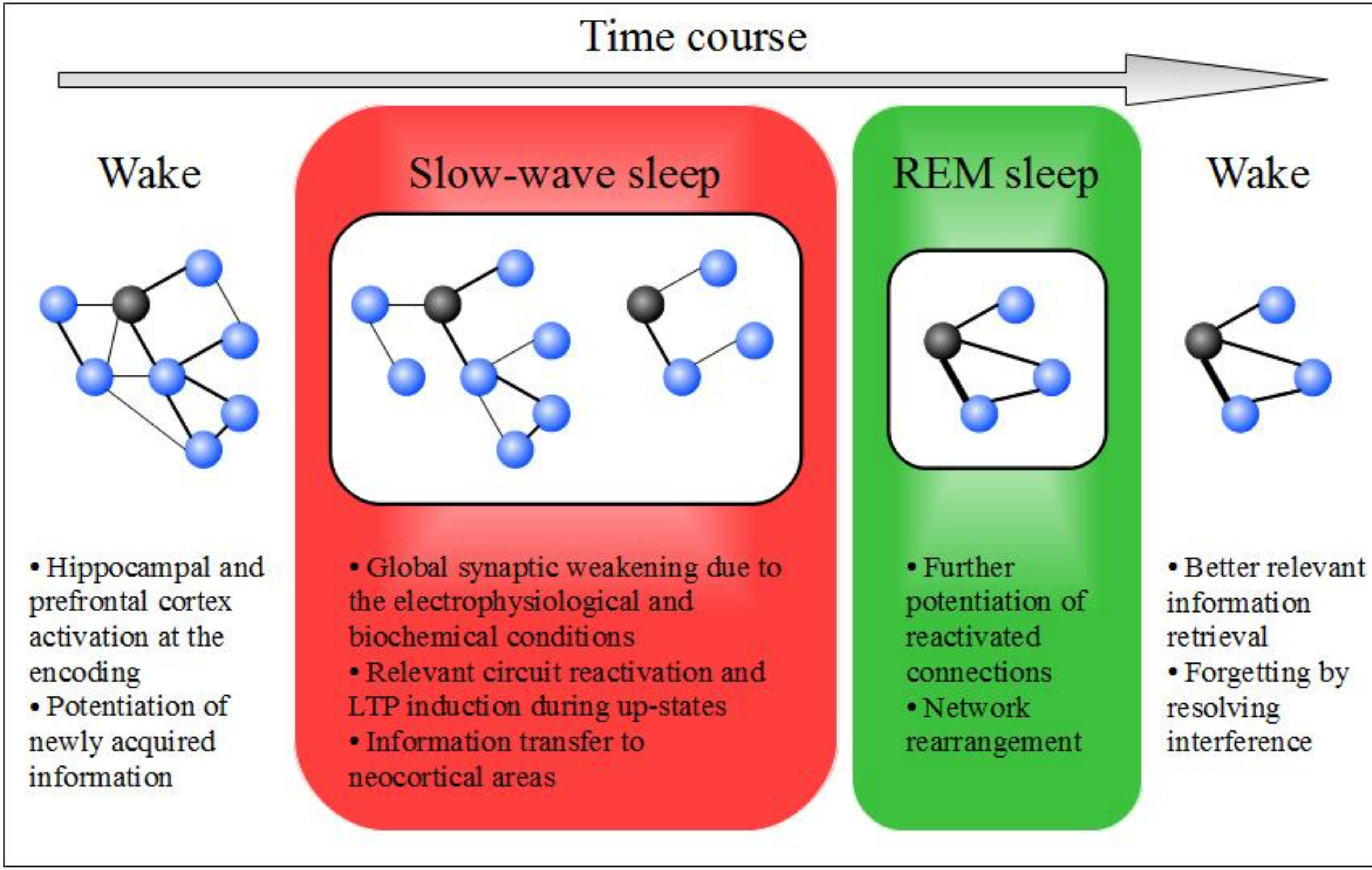
Characteristic patterns of the brain activities in the neocortex and hippocampus

	Awake	Non-REM sleep			REM sleep
		Stage 1	Stage 2	Stage 3-4	
Cortex	Alpha wave Gamma wave		Spindle K complex	Delta wave Theta wave	Gamma wave
Hippocampus	Theta wave HVS	High-voltage spike (HVS) with high-frequency ripple (~200 Hz)			Theta wave

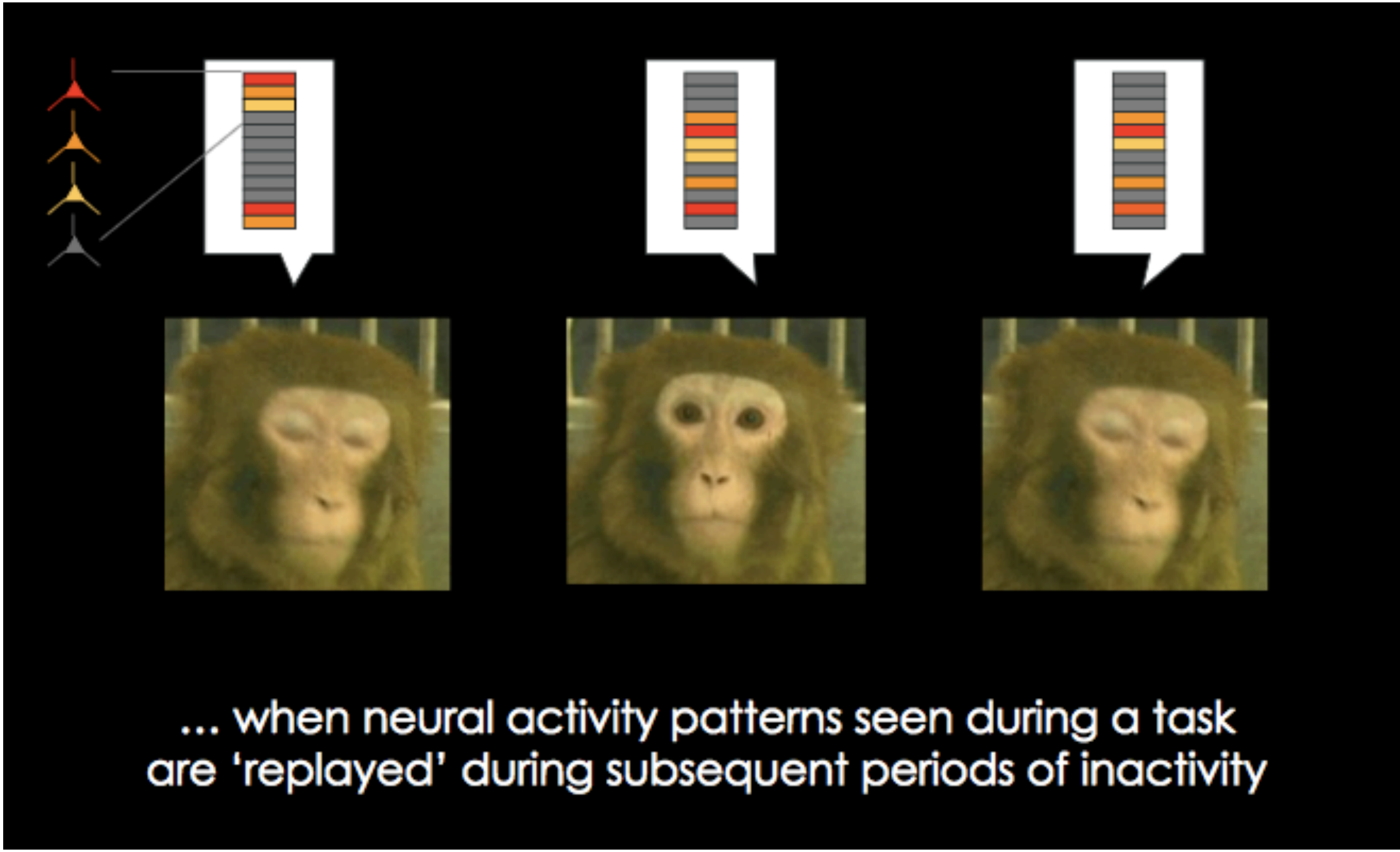
Buzsaki, *Neuroscience*, 31, 551-70, 1989.
Gottesmann, *Neurosci. Biobehav. Rev.*, 16, 31-8, 1992.
Steriade et al., *Science*, 262, 679-85, 1993.
Steriade, *Neuroscience*, 101, 243-76, 2000.

slow oscillation from the neocortex
spindle from the thalamus
ripple from the hippocampus

Does sleep prevent or promote forgetting?



Sleep and Memory Formation



Sleep, and Memory formation
Reactivation

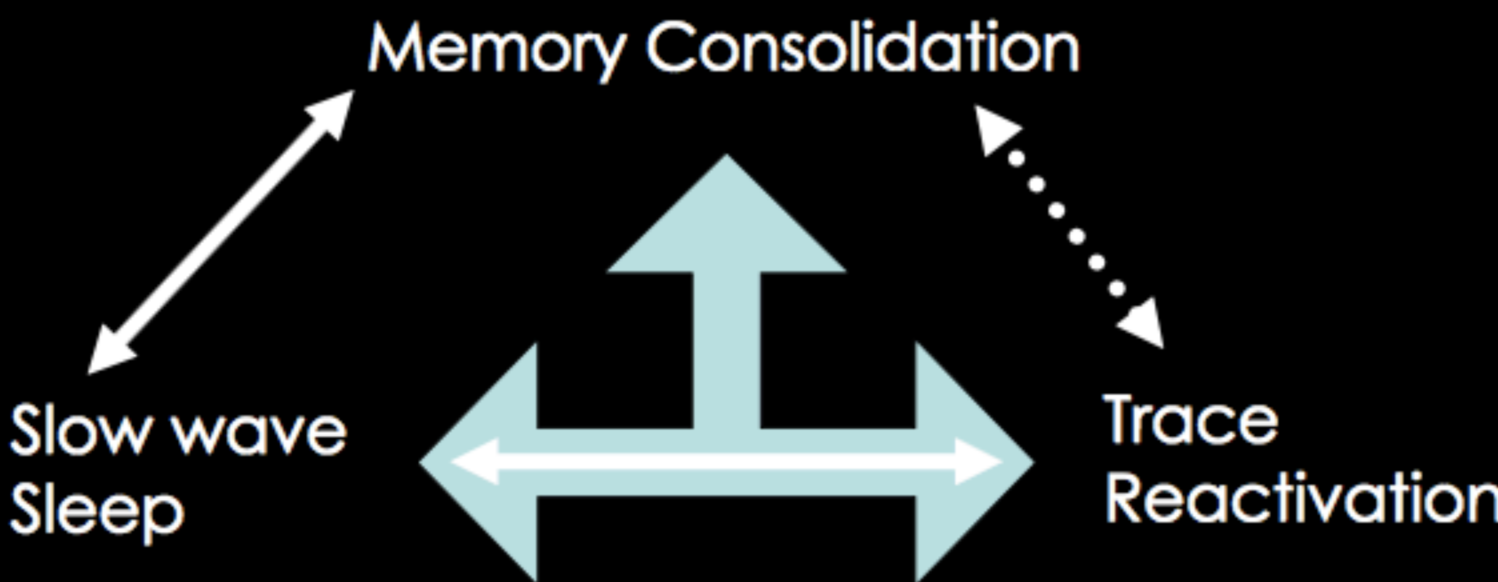
- In rats, hippocampal activity patterns during behavior are related to patterns during subsequent periods of inactivity (Pavlides and Winson, 1989; Wilson and McNaughton, 1994),
  - specifically, in hippocampal oscillations (Kudrimoti et al., 1999)
  - demonstrated to co-occur with slow-waves (Sirota et al., 2003; Battaglia et al., 2004)

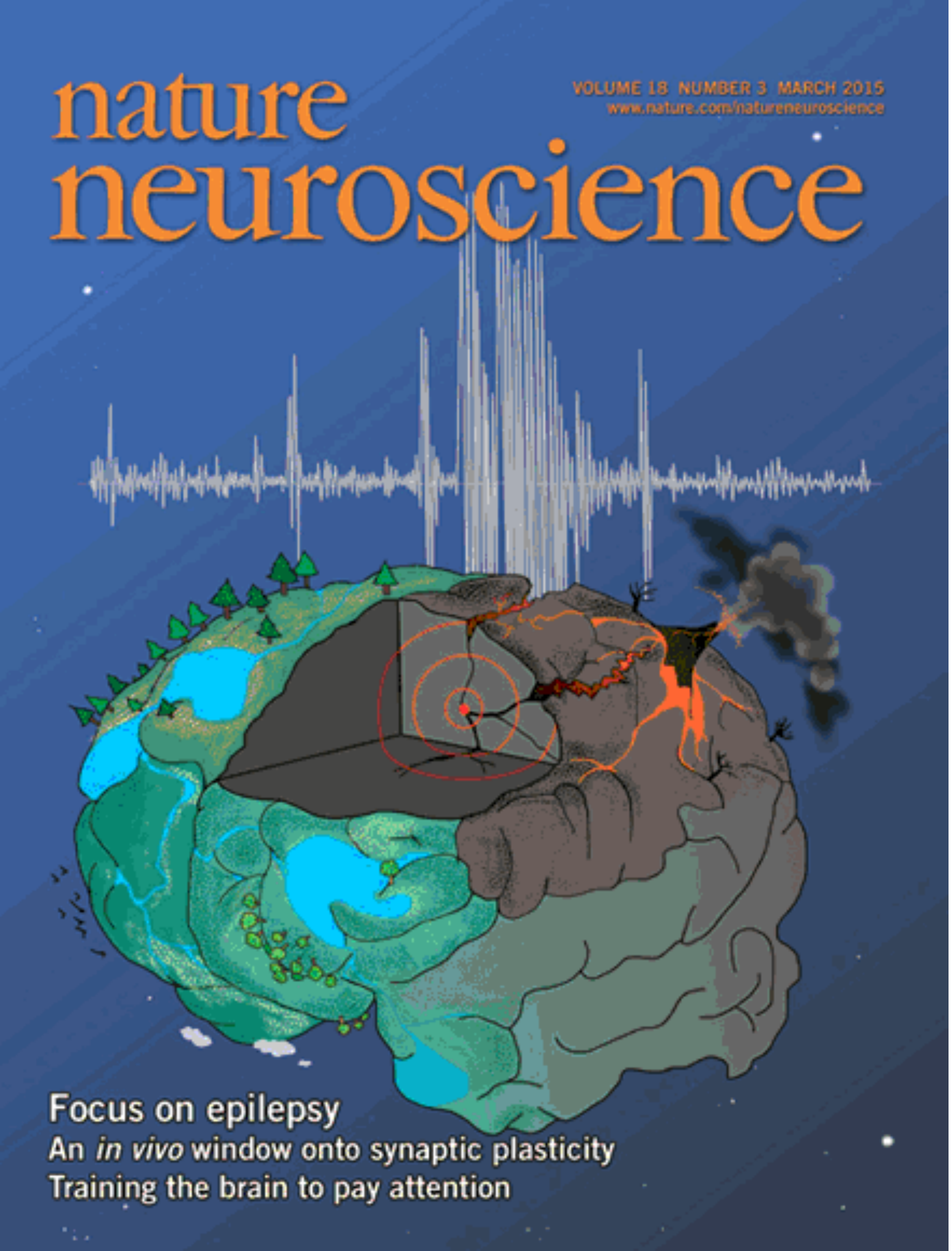
- seen in the hippocampus and neocortex of rats (Qin et al., 1997; Ribeiro et al., 2004; Ji and Wilson, 2007)

- seen in non-human primate, in multiple 'disconnected' sites, coordinated across hemispheres. (Hoffman and McNaughton, 2002)

- seen in other structures, maybe under other names (Arieli, Yuste/MacLean, Dan)

The upshot of up states in neocortex: From slow oscillations to memory formation





Epilepsy: disorder of brain dynamics

- Characterized by recurrent seizures
- Associated with abnormally excessive or synchronous neuronal activity

Current Treatment:

- Anti-Epileptic Drugs *(undesirable side effects)*
- Surgical Removal of Tissue

Motivation for Seizure Prediction:

- Increase quality of life of epilepsy sufferers

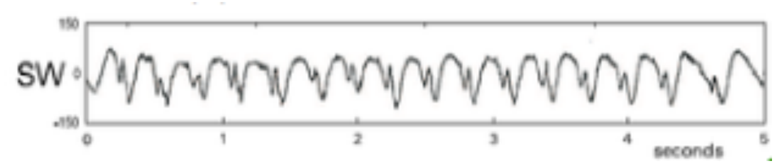
A robust seizure prediction algorithm requires ***machine learning.***

Epilepsy

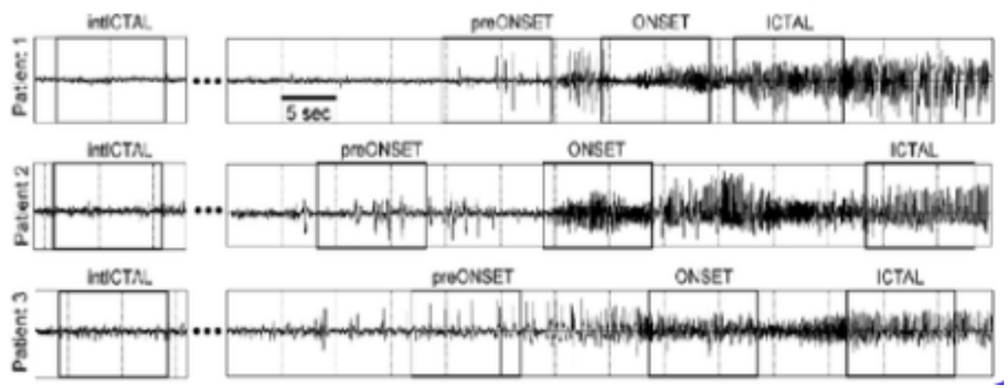
Epilepsy
Chronic Illness
Affects 1% to 2% of world population
40% of patients refractory to medication
Surgery available as treatment

Partial ("focal")
Chronic Illness
Affects 1% to 2% of world population
40% of patients refractory to medication
Surgery available as treatment

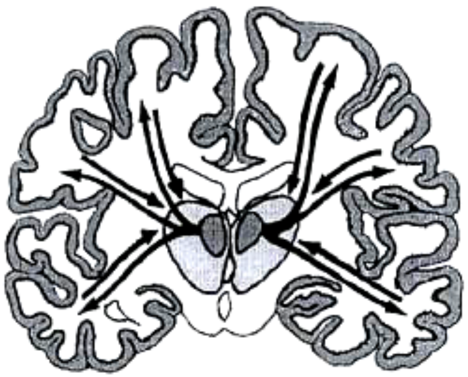
Generalized: Absence "petit mal"
Impairment of consciousness
Abrupt start and termination
Short duration
Unpredictable

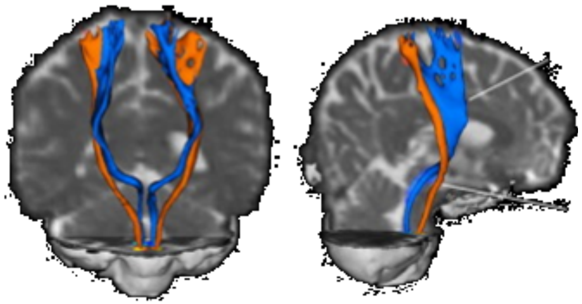


Generalized: Tonic-Clonic ("grand mal")
Rhythmic muscle contractions
Loss of consciousness



Childhood Absence Epilepsy



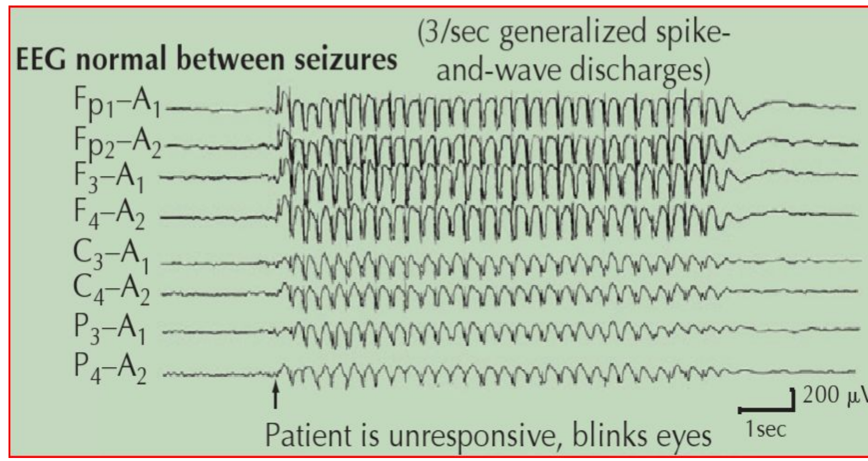


Pathophysiology of an Absence Seizure

<u>*On Left*</u>**:** *Corticoreticular Theory.*

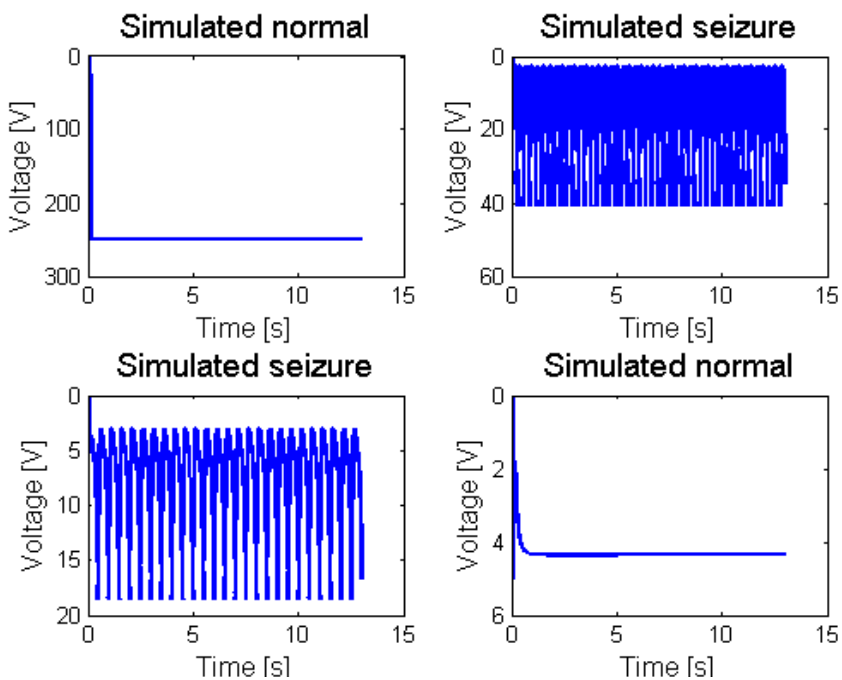
Focal point or initiation site of absence seizure is in somatosensory cortex. Rhythmic oscillations between cortex and thalamus drive each other to propagate the spike-wave discharges of an absence seizure.

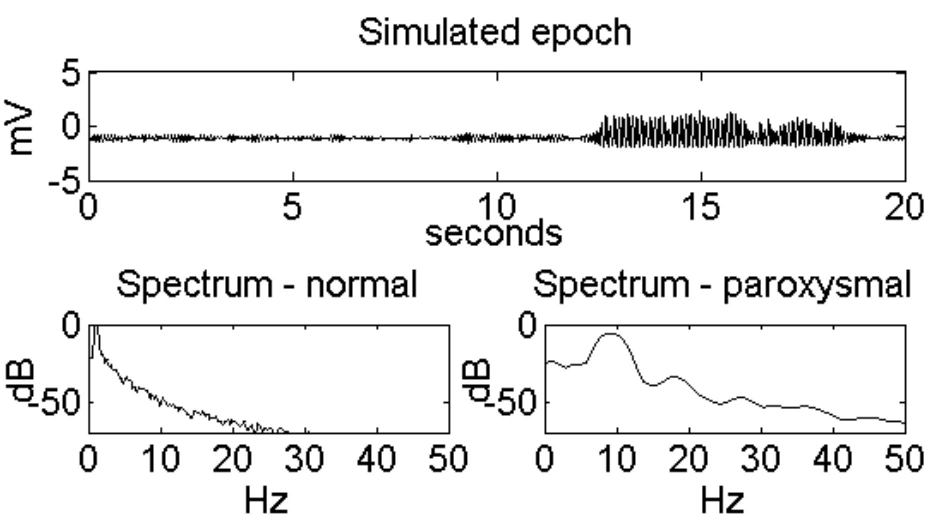
<u>*On Right*</u>*: Oscillations are proposed to propagate along the corticoreticular pathway (blue).*



Clinical Presentation:
Distinct high-amplitude, bilateral synchronous, symmetric, 3 – 4 Hz spike-and-wave discharges of absence seizure.

Models of Epilepsy: Animal and Computational





Animal Models of Epilepsy

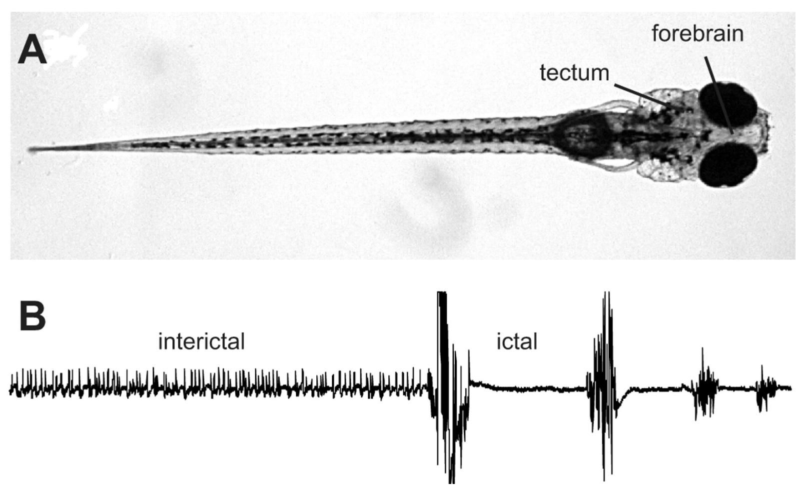
Species	***Drosophila melanogaster (fruit fly)***	***Danio rerio (zebra fish)***	***Mus musculus (mouse)***	***Canis familiaris (dog)***	***Papio hamadryas (baboon)***
First epilepsy studies	Dynamin mutant	Pentylene-tetrazole	Audio-genic	Electro convulsive	Photosensitive
Number of neurons	100,000	100,000 (larvae)	71,000,000	160,000,000 (cortex)	11,000,000,000
Percentage of human genes	39%	63%	79%	81%	93%
Cost per day	<$0.01	~$0.01	~$0.20	$27.30	$19.75

Genetic Models of Seizures:

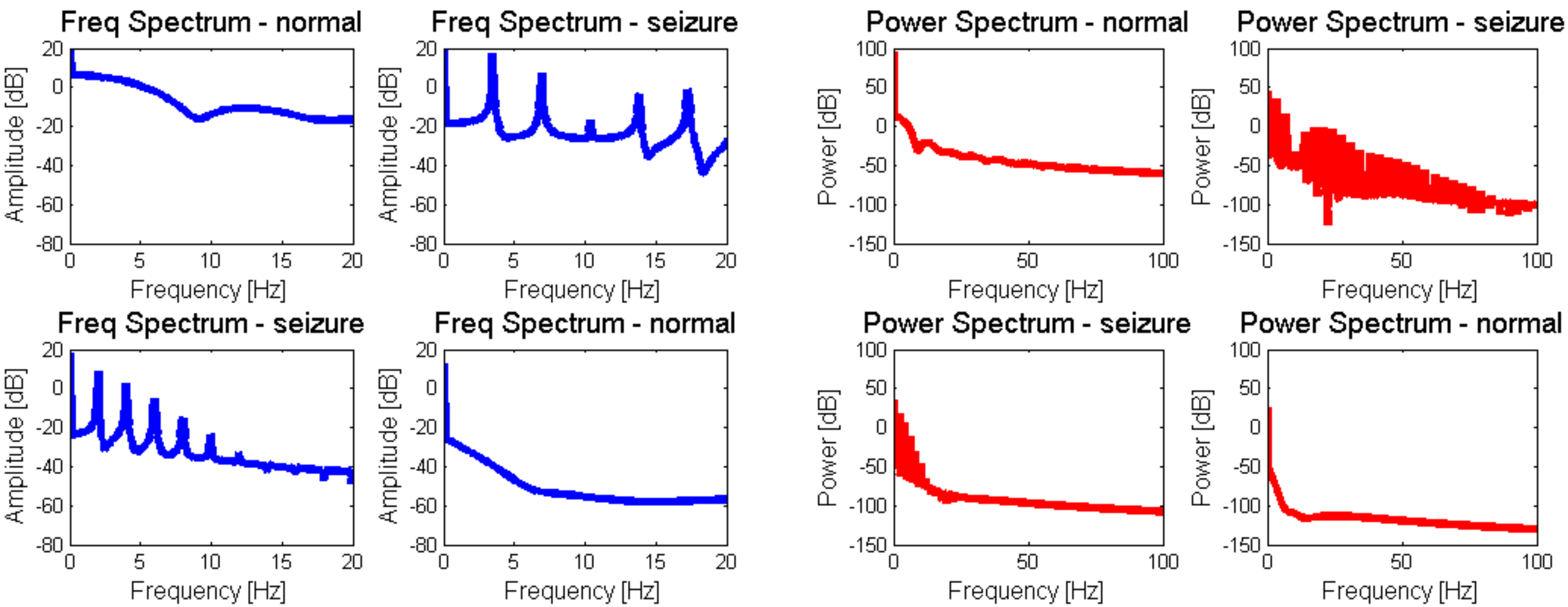
- Knockdown of genes
- SCN1A Mutants

Non-Genetic Models of Seizures:

- Kainic acid (activates receptors for glutamate)
- Pilocarpine (compromises the blood-brain barrier)



Computational Model of Absence Epilepsy



On Left: Frequency Spectrum of Epilepsy Simulation

There is intense activity in the 2-4 Hz range from bottom left graph, and the top right graph shows a peak at 3.47 Hz.

On Right: Power Spectrum of Epilepsy Simulation

It is clear to note the differences between normal data and seizure data visually as evident by spiking patterns. A seizure prediction algorithm can be based on energy analysis in frequency bandwidths of interest.

Amplitude v. Frequency *with Fourier Transform provides* **Power v. Frequency**

Approaches to the problem

Feature extraction from EEG:

Linear

System of noise-driven linear equations

$$y(t) = ax(t) + b + \eta(t)$$

Non-linear

Deterministic dynamical system of nonlinear equations

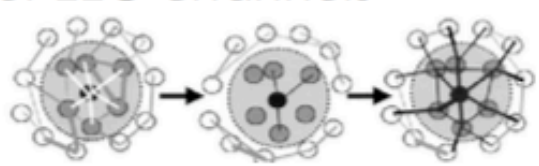
Relationship between EEG channels:

Univariate

1 channel at a time

Bivariate

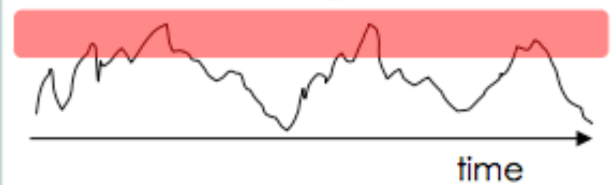
Varying synchronization of EEG channels



Classification based on:

Statistics

Discriminating measure

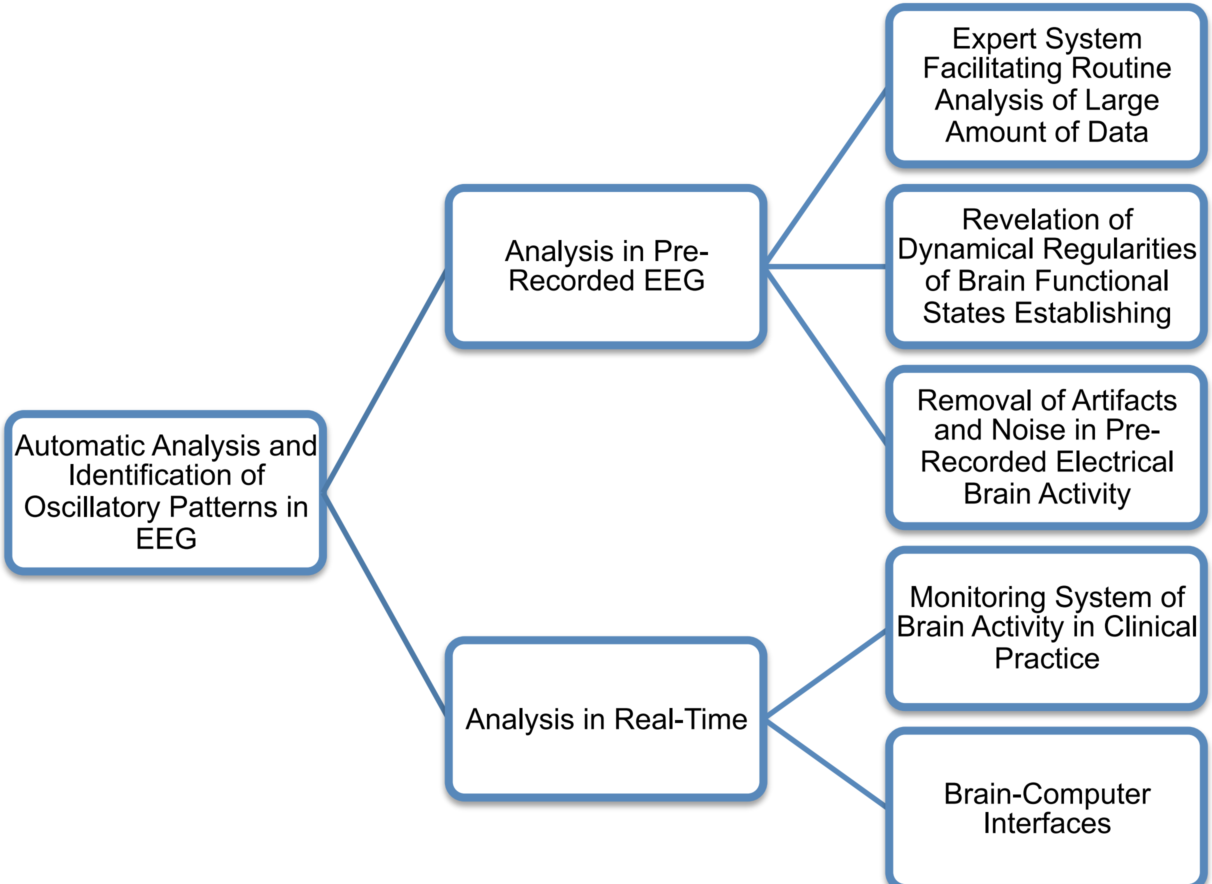


Algorithm

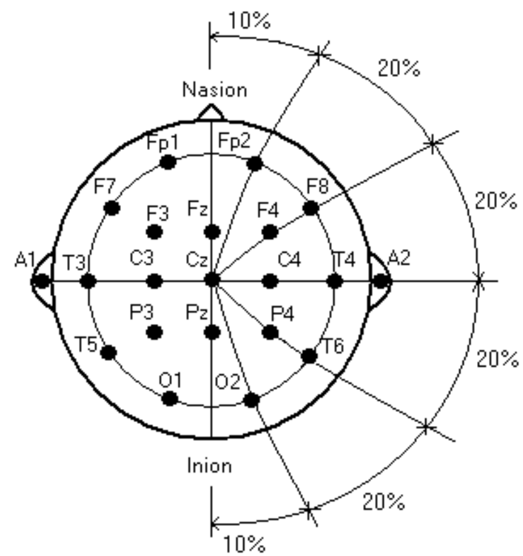
Machine Learning: neural networks, genetic optimization…

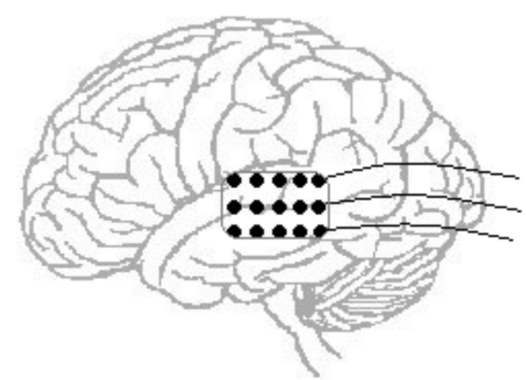
Slide by Yann LeCun

Analysis of Electroencephalogram (EEG) Data



EEG Data: recordings of the fluctuating electric fields of the brain





Flowchart: Review of methods available for EEG analysis

<u>On Right:</u>

Top: Scalp EEG data

Bottom: Intracranial grid EEG data

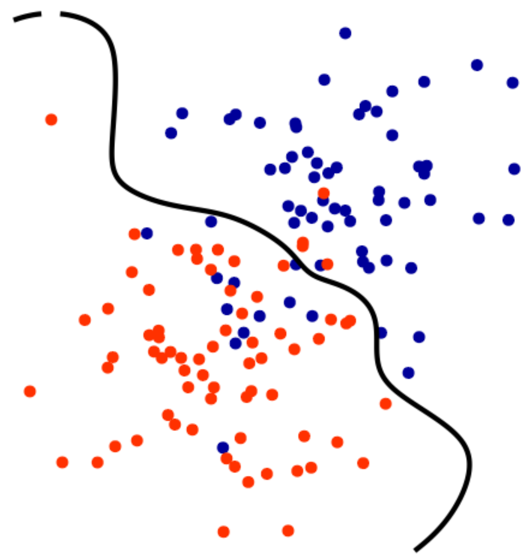
The Seizure Prediction Problem

Review of Literature:

- Most methods implement 1D decision boundary
- Machine learning used only for feature selection

Trade-off Between:

- Sensitivity (being able to predict seizures)
- Specificity (avoiding false positives)

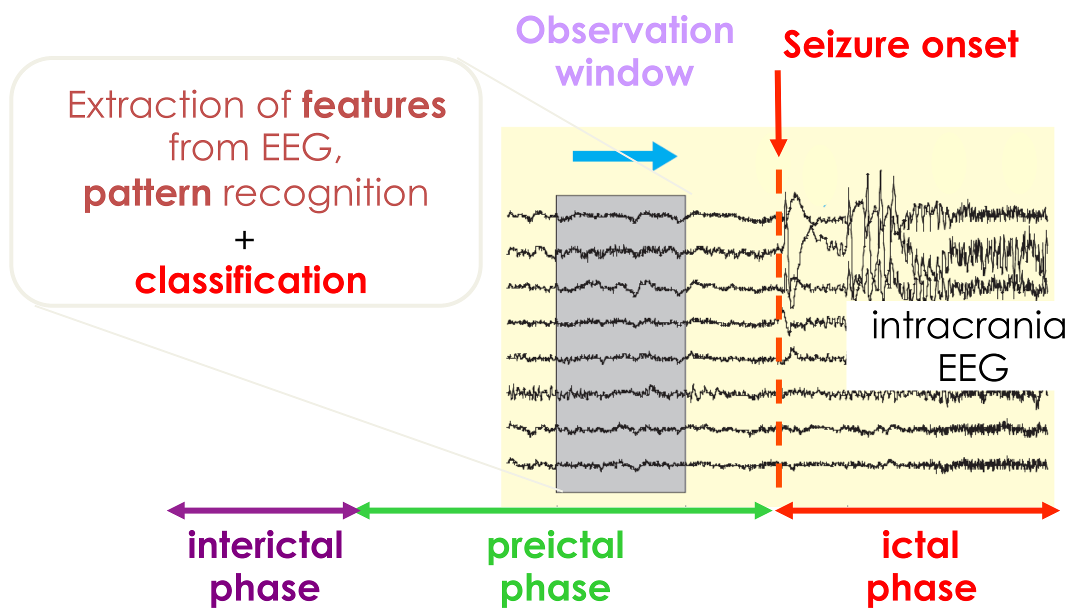


A decision boundary is the region of a problem space in which the output label of a classifier is ambiguous.

Interictal phase: period between seizures, or convulsions, that are characteristic of an epilepsy disorder

Preictal phase: state immediately before the actual seizure

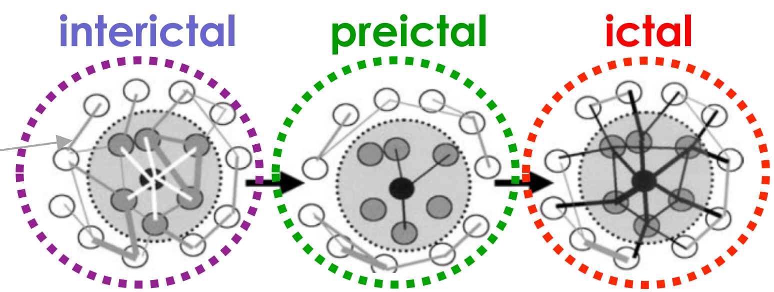
Ictal phase: physiologic state of seizure
(Latin: ictus, meaning a blow or a stroke)



Hypotheses

- patterns of brainwave synchronization:
  - could **differentiate preictal** from **interictal** stages
  - would be **unique** for each epileptic **patient**

- definition of a "**pattern**" of brainwave synchronization:
  - collection of bivariate "**features**" derived from EEG,
  - on **all pairs of EEG channels** (focal and extrafocal)
  - taken at **consecutive time-points**
  - capture transient changes



- a bivariate "**feature**":
  - captures a **relationship**:
  - over a short time window

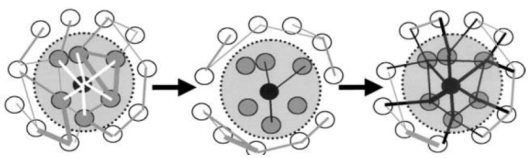
- goal: **patient-specific automatic learning to differentiate preictal and interictal patterns of brainwave synchronization features**

[Le Van Quyen et al, 2003; Mirowski et al, 2009]

Slide by Yann LeCunn

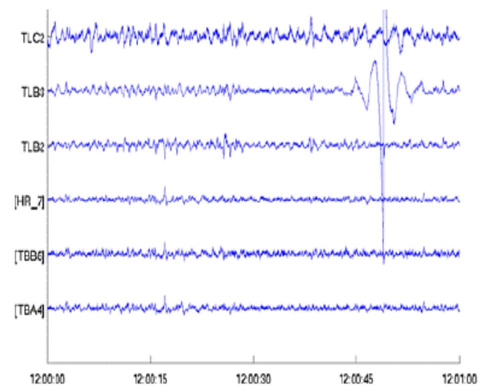
Patterns of bivariate features

Varying synchronization of EEG channels

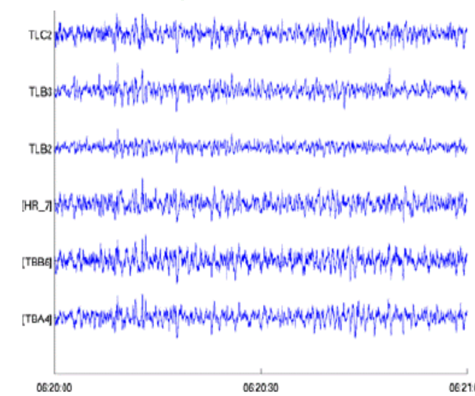


- Non-frequential features:
  - Max cross-correlation [Mormann et al, 2005]
  - Nonlinear interdependence [Arhnold et al, 1999]
  - Dynamical entrainment [Iasemidis et al, 2005]
- Frequency-specific features: [Le Van Quyen et al, 2005]
  - Phase locking synchrony
  - Entropy of phase difference
  - Wavelet coherence

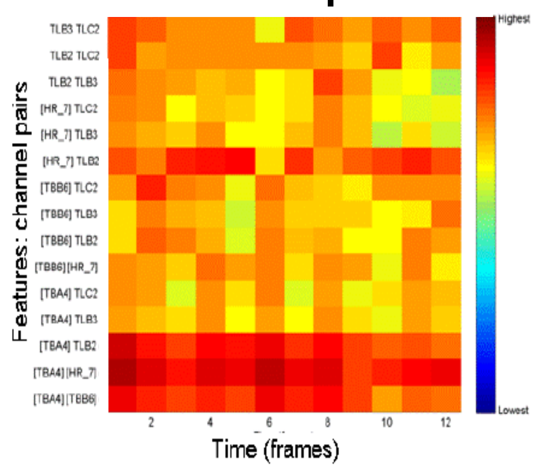
1min of interictal EEG



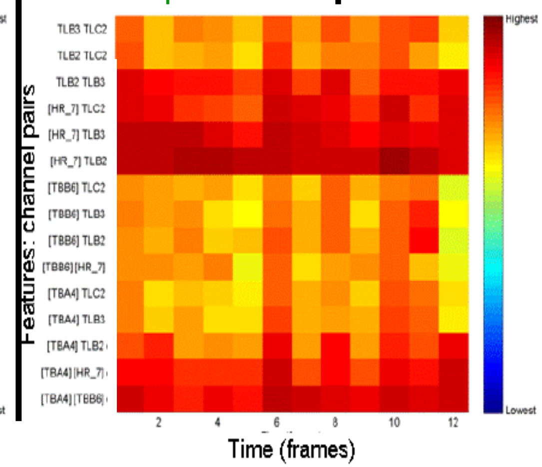
1min of preictal EEG



1min interictal **pattern**



1min preictal **pattern**

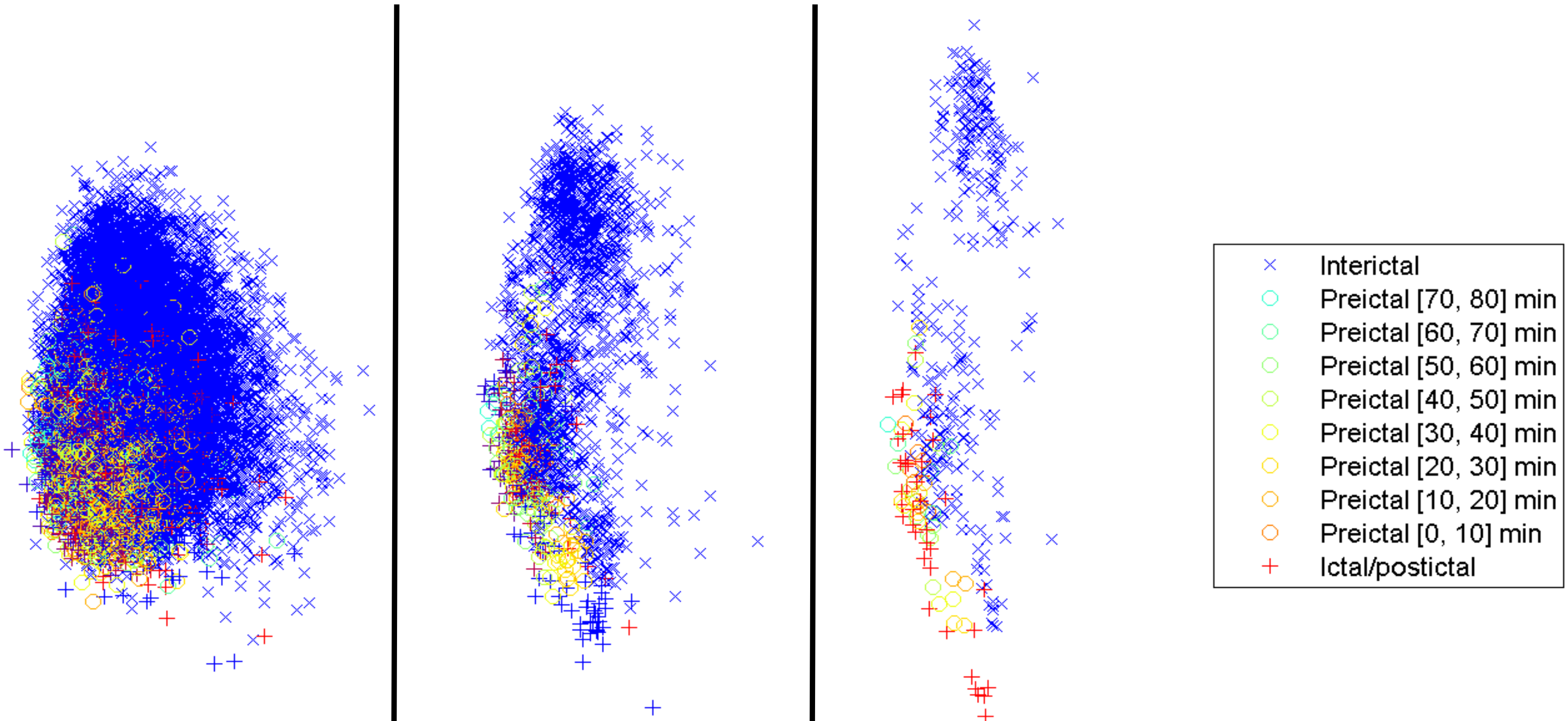


Examples of **patterns** of **cross-correlation**

[Le Van Quyen et al, 2003; Mirowski et al, 2009]

Slide by Yann LeCunn

Separating patterns of features

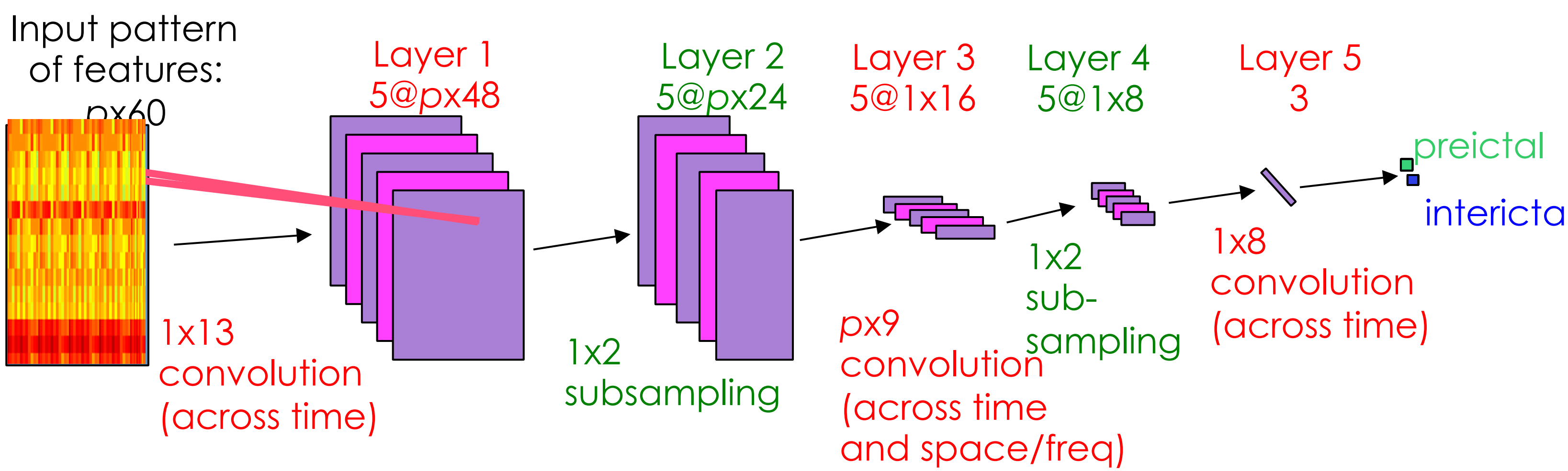


a) 1-frame patterns (5s) **b) 12-frame patterns (1min)** **c) 60-frame patterns (5min)** **d) Legend**

2D projections (PCA) of wavelet synchrony SPLV features, patient 1

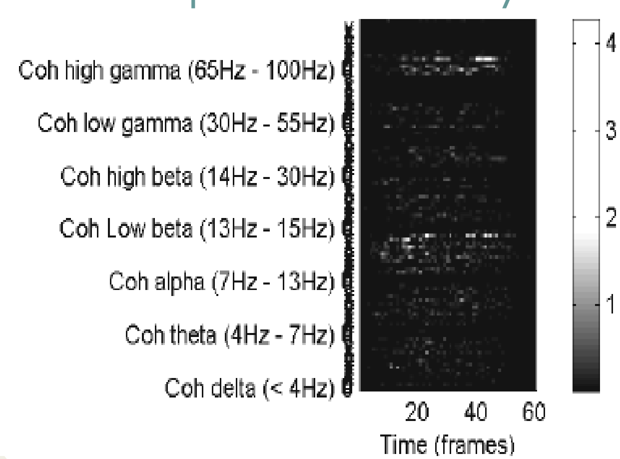
[Mirowski et al, 2009]

Slide by Yann LeCunn



- L_1-regularized **convolutional networks** (LeNet5, above)
- L_1-regularized **logistic regression**
- **Support vector machines** (Gaussian kernels)
- L1-regularization highlights pairs of channels and frequency bands discriminative for seizure prediction

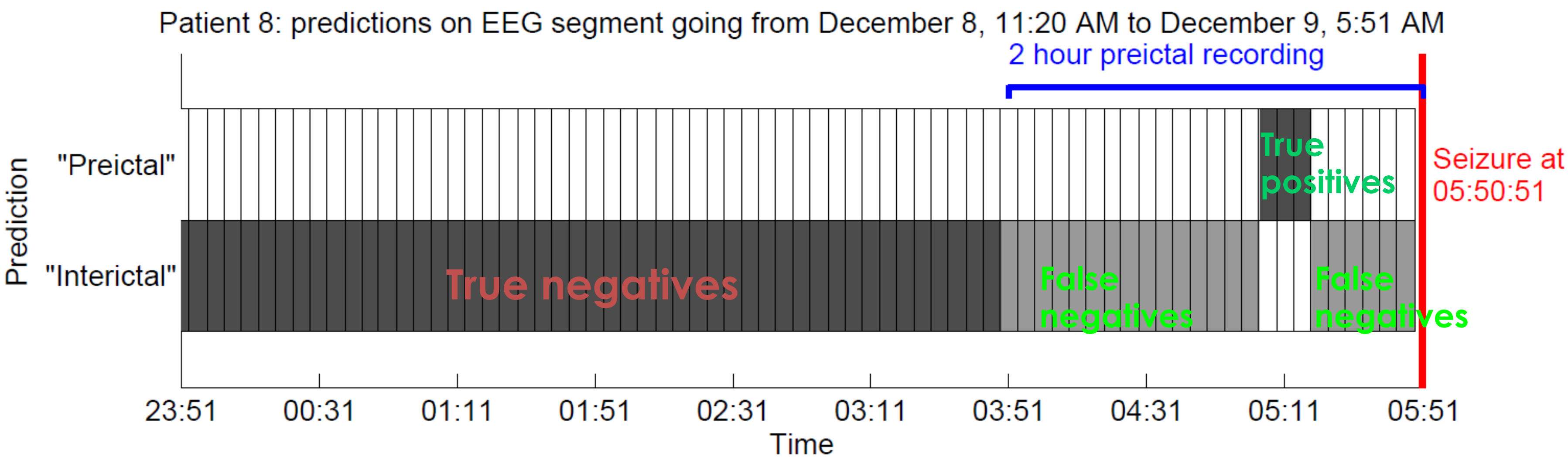
Input sensitivity



[LeCun et al, 1998; Mirowski et al, AAAI 2007, 2009]

Slide by Yann LeCunn

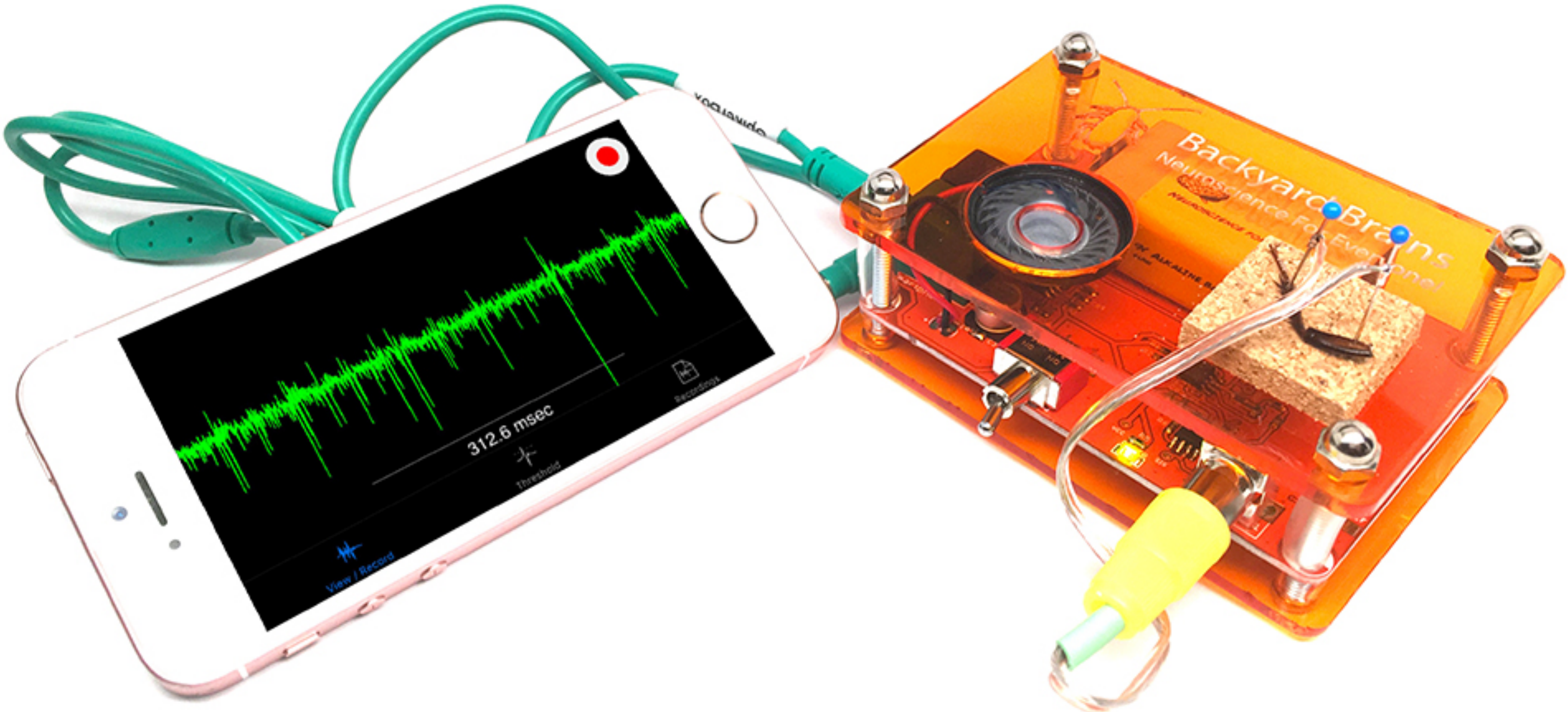
Example of Seizure Prediction



	Hypothesis: Patient has seizure.	**Null Hypothesis: Patient does not have seizure.**
Reality: Patient does not have seizure.	Type I Error (model predicts seizure but patient does NOT have seizure) **False Positives**	Correct Outcome (model predicts no seizure and patient does NOT have seizure) **True Negatives**
Reality: Patient has seizure.	Correct Outcome (model predicts seizure and patient does have seizure) **True Positives**	Type II Error (model predicts no seizure but patient does have seizure) **False Negatives**

Next Time:

Biophysical Models of Neurons



Please bring laptops for programming demo with SpikerBoxes