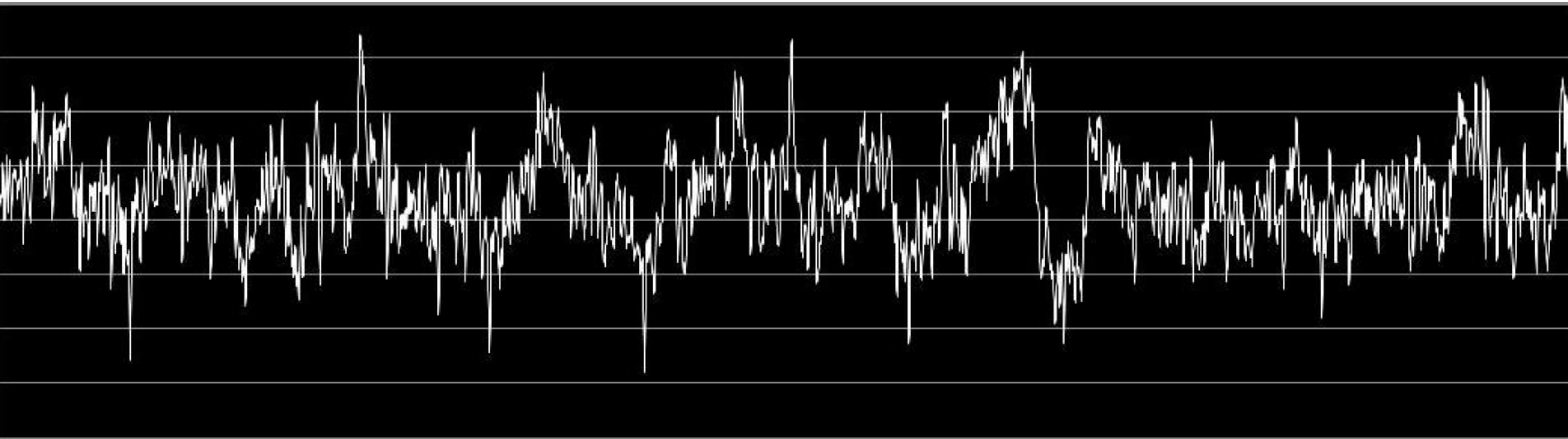
# Applied Neuroscience

## Columbia Science Honors Program

## Fall 2016

### Computational Models of Psychiatric Disorders

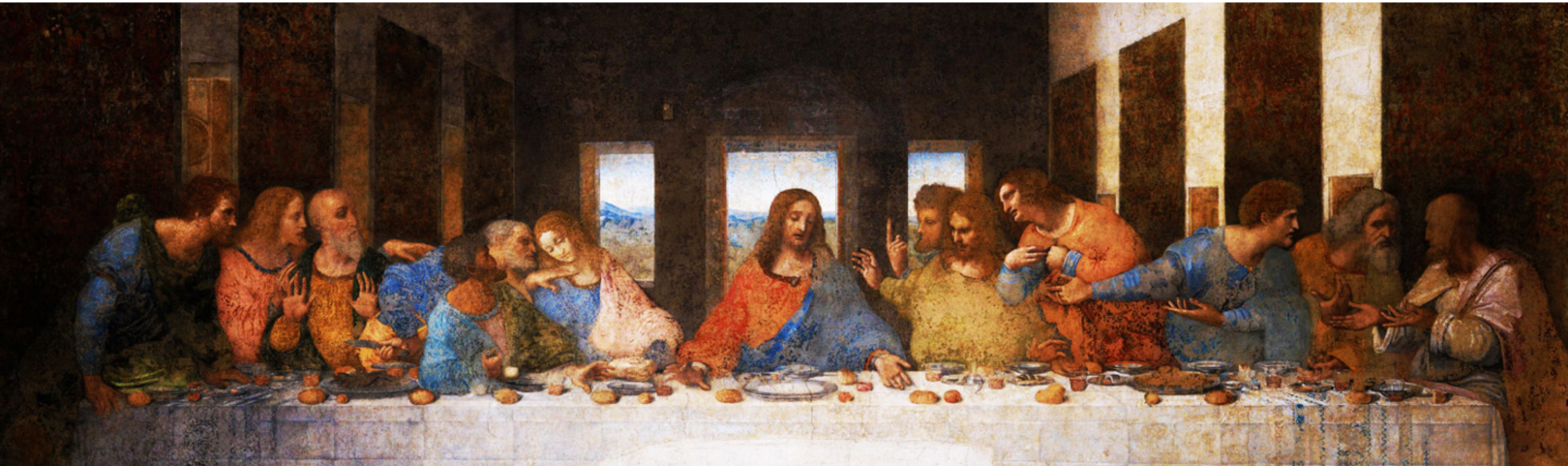


# Psychiatric Disorders

**Objective:** Role of Computational Models in Psychiatry

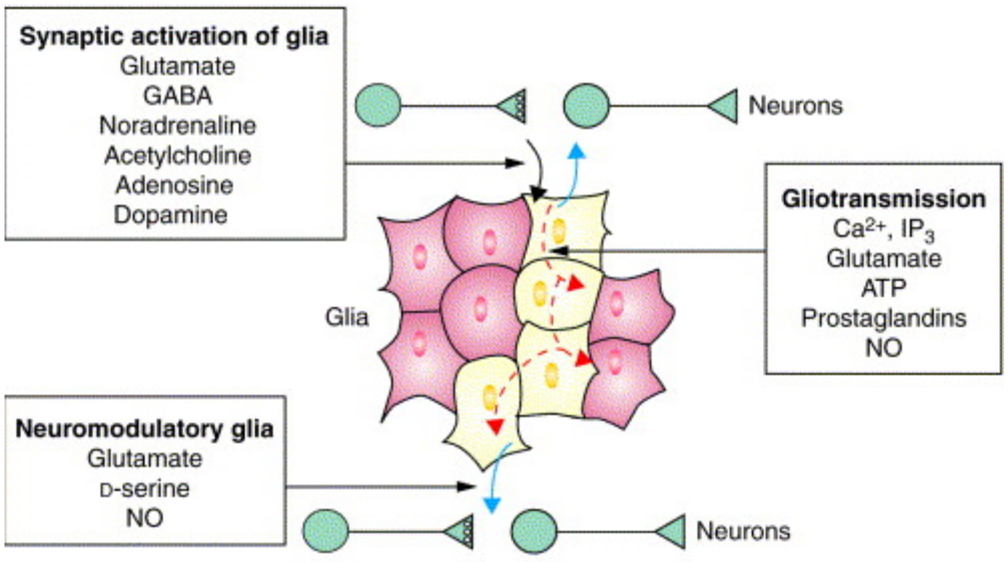
**Agenda:**

1. Modeling Spikes and Firing Rates
   - *Overview*
   - *Guest Lecture by Evan Schaffer and Sean Escola*
2. Psychiatric Disorders
   - *Epilepsy*
   - *Schizophrenia*
3. Conclusion



# Why use models?

- Quantitative models force us to think about and formalize hypotheses and assumptions
- Models can integrate and summarize observations across experiments and laboratories
- A model done well can lead to *non-intuitive* experimental predictions
- A quantitative model, implemented through simulations, can be useful from an engineering standpoint
  *i.e. face recognition*
- A model can point to important missing data, critical information, and decisive experiments




**Case Study: Neuron-Glia Signaling Network in Active Brain**

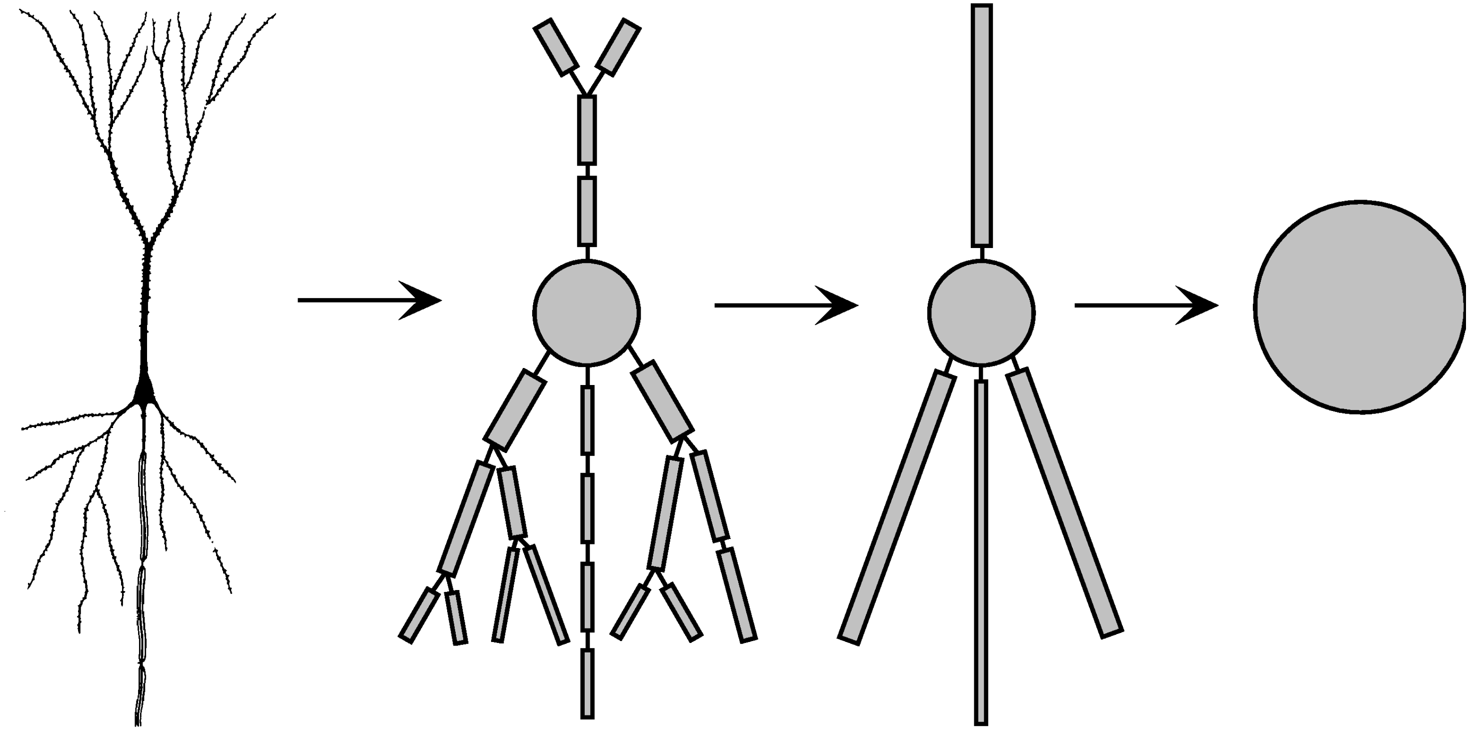
*Chemical signaling underlying neuron-glia interactions. Glial cells are believed to be actively involved in processing information and synaptic integration. This opens up new perspectives for understanding the pathogenesis of brain diseases. For instance, inflammation results in known changes in glial cells, especially astrocytes and microglia.*

# Single Neuron Models

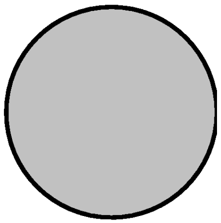
***Central Question:*** What is the correct level of abstraction?

- Filter Operations
- Integrate-and-Fire Model
- Hodgkin-Huxley Model
- Multi-Compartment Models
- Models of Spines and Channels

*Abstract thought depicted in Inside Out by Pixar.*



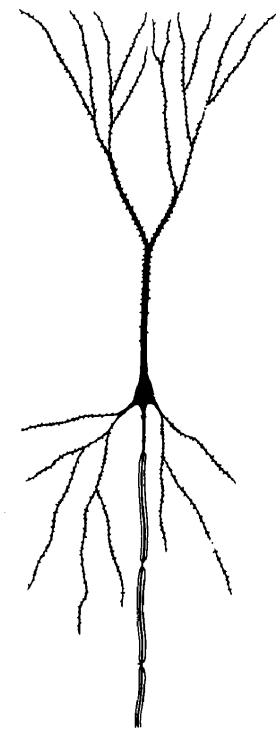
# Single Neuron Models



**Artificial Neuron Model:** aims for computational effectiveness and consists of

- an input with some synaptic weight vector
- an activation function or transfer function inside the neuron determining output

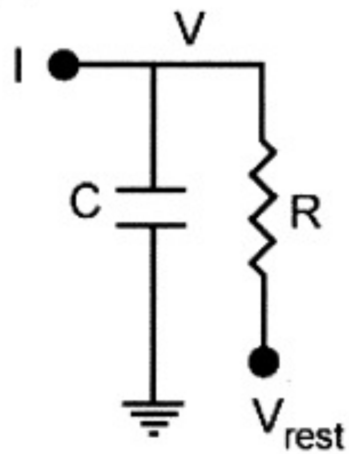
$$O_j = f(\sum w_{ij} e_i)$$



**Biological Neuron Model:** mathematical description of the properties of neurons

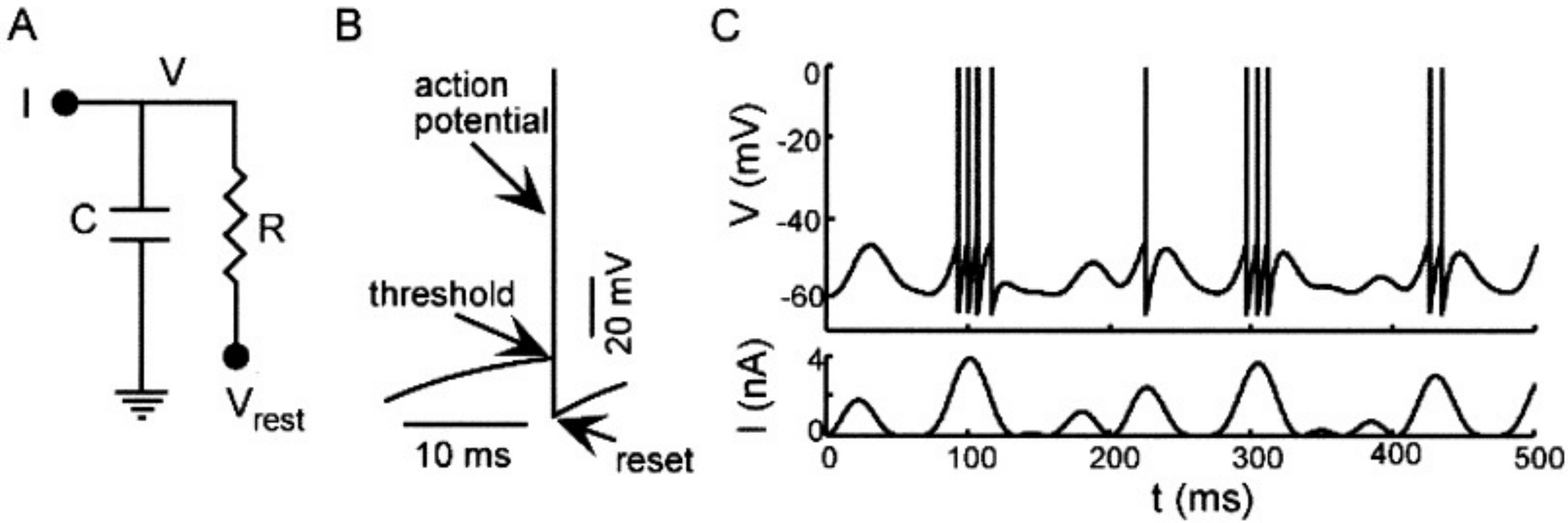
- physical analogs are used in place of abstractions such as “weight” and “transfer function”
- ion current through the cell membrane is described by a physical time-dependent current *I(t)*
- Insulating cell membrane determines a capacitance $C_m$
- A neuron responds to such a signal with a change in voltage, resulting in a voltage spike (action potential)

# Integrate-and-Fire Neuron Model

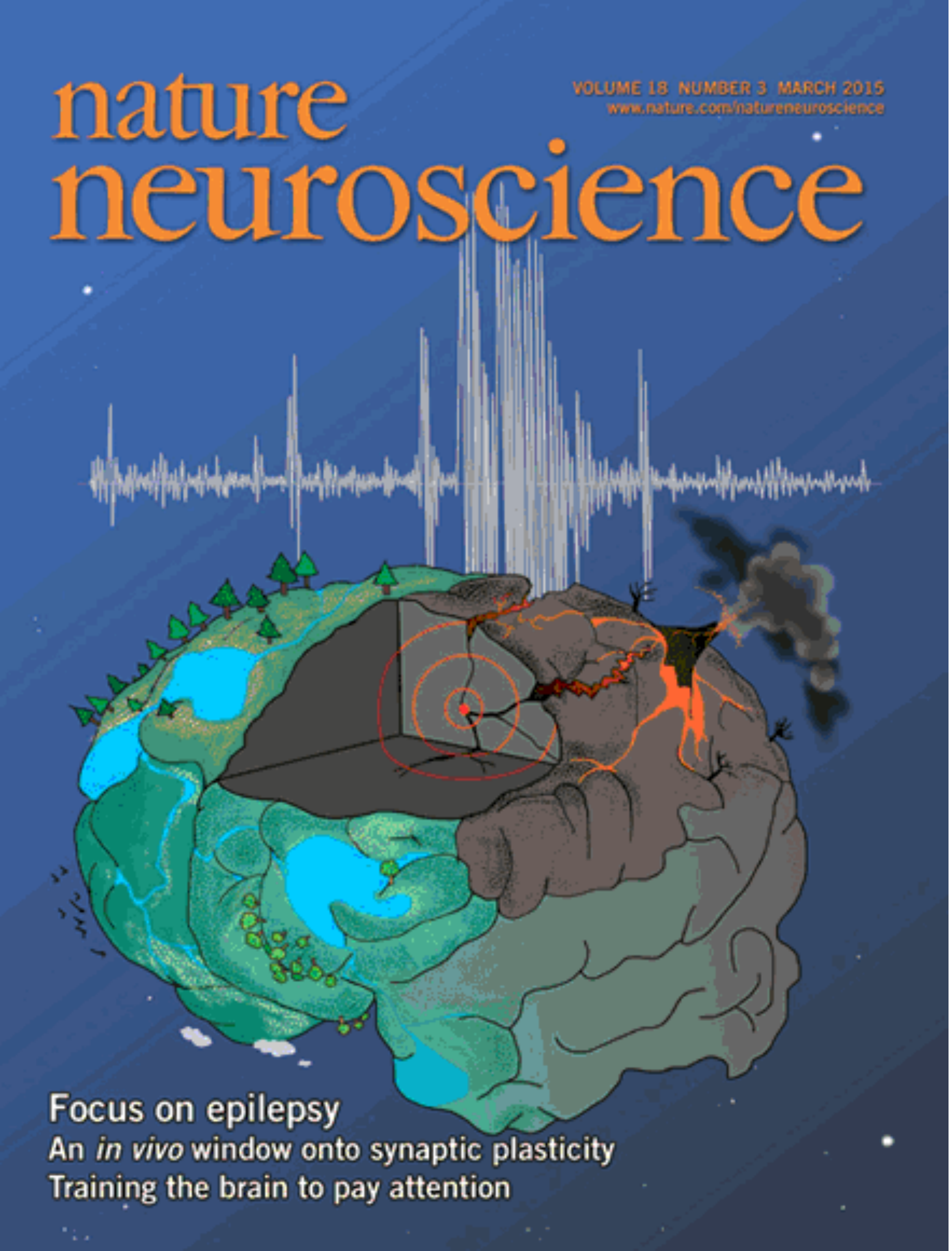



- Proposed in 1907 by Louis Lapicque
- Model of a single neuron using a circuit consisting of a parallel capacitor and resistor
- When the membrane capacitor was charged to a certain threshold potential
  - an action potential would be generated
  - the capacitor would discharge
- In a biologically realistic neuron model, it often takes multiple input signals in order for a neuron to propagate a signal.
- Every neuron has a certain threshold at which it goes from stable to firing.
- When a cell reaches its threshold and fires, its signal is passed onto the next neuron, which may or may not cause it to fire.
- *Shortcomings of Model:*
  - an input, which may arise from pre-synaptic neurons or from current injection, is integrated linearly, independently of the state of post-synaptic neuron
  - no memory of previous spikes is kept

# Integrate-and-Fire Neuron Model




A. The equivalent circuit with membrane capacitance *C* and resistance *R*. *V* is the membrane potential, $V_{rest}$ is the resting membrane potential, and *I* is an injected current.
B. Voltage trajectory of the model. When *V* reaches a threshold value, an action potential is generated and *V* is reset to a sub-threshold value.
C. Integrate-and-fire model neuron driven by a time-varying current. Upper trace is membrane potential and bottom trace is input current.




**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.***

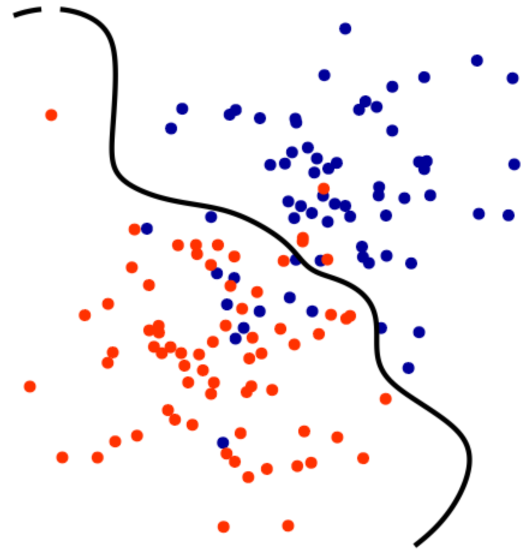
# The Seizure Prediction Problem

## 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)

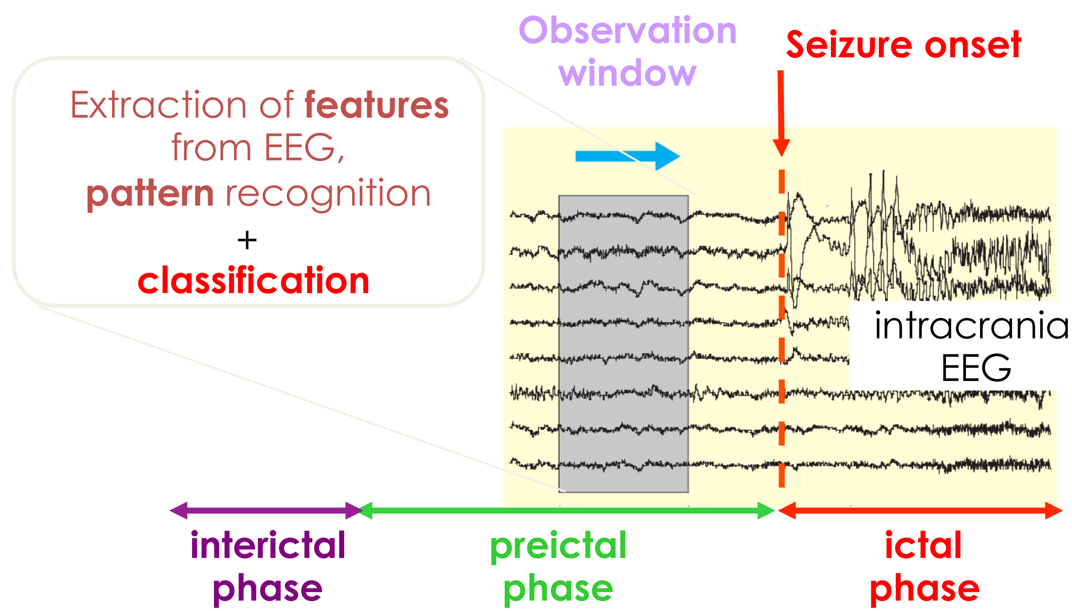


*A decision boundary is the region of a problem space in which the output label of a classifier is ambiguous.*

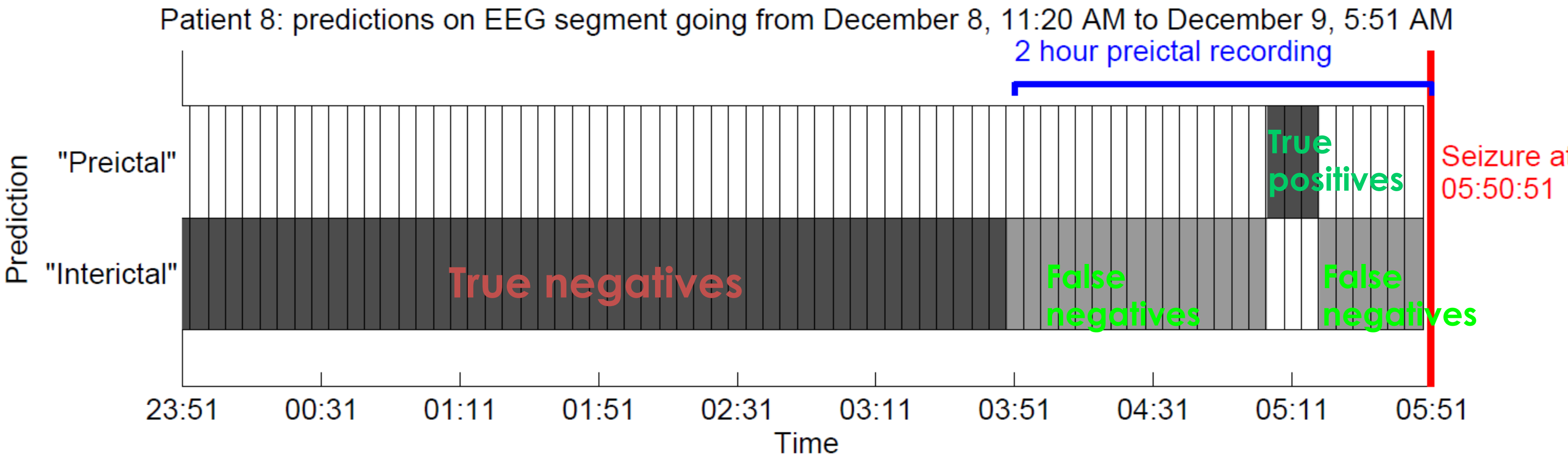
**Interictal phase: period between seizures, or convulsions, that are characteristic of an epilepsy disorder**

**Preictal phase: state immediately before the actual seizure**

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

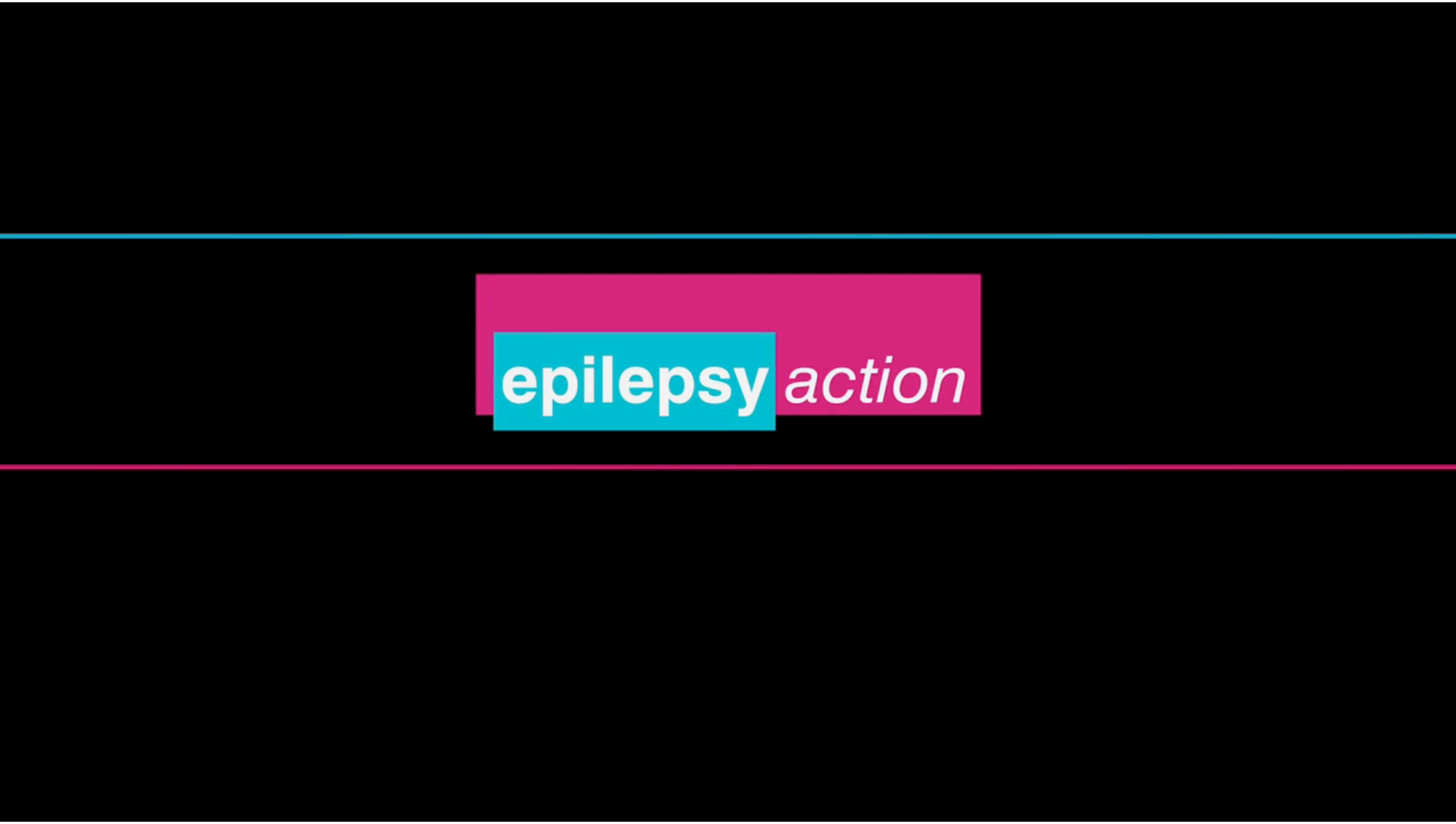


# Example of Seizure Prediction

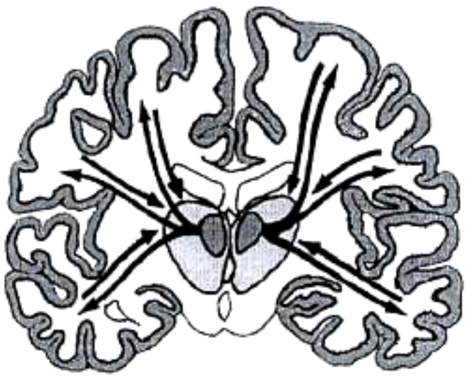


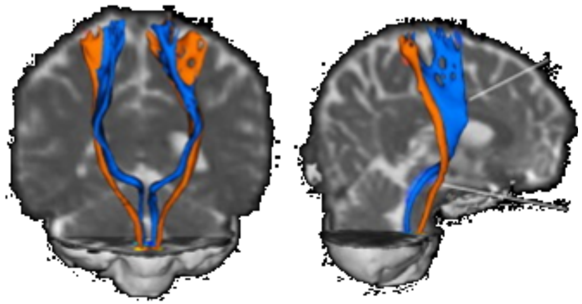

| | **Hypothesis: Patient has seizure.** | **Null Hypothesis: Patient does not have seizure.** |
|---|---|---|
| Reality: Patient does not have seizure. | Type I Error (model predicts seizure but patient does NOT have seizure) **False Positives** | Correct Outcome (model predicts no seizure and patient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

# Childhood Absence Epilepsy



# Childhood Absence Epilepsy



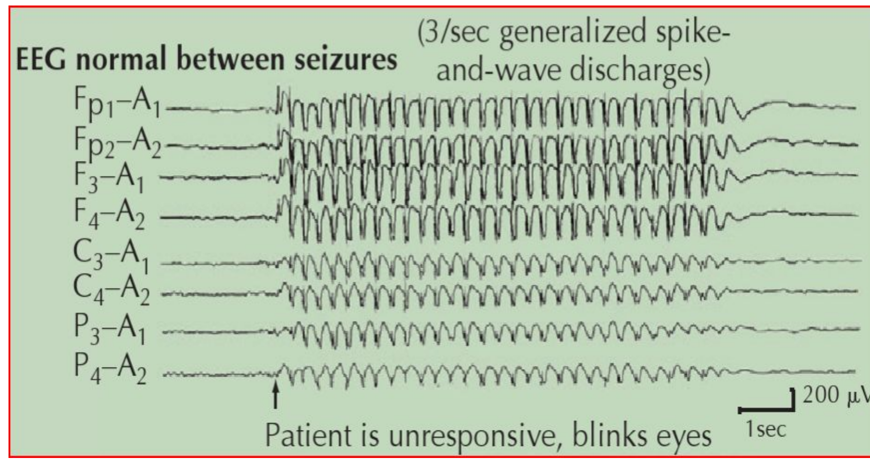


## Pathophysiology of an Absence Seizure

*<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.*

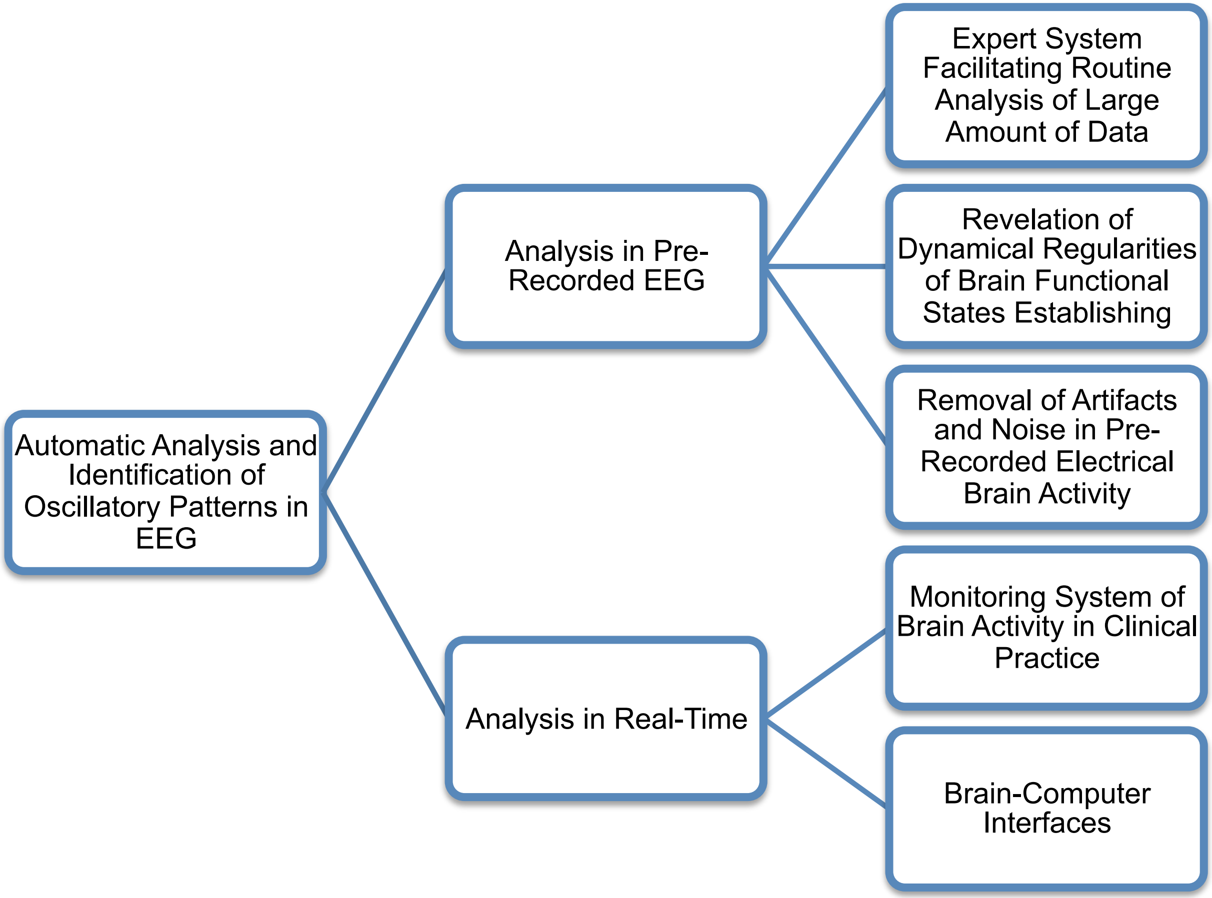
*<u>On Right</u>: Oscillations are proposed to propagate along the corticoreticular pathway (blue).*



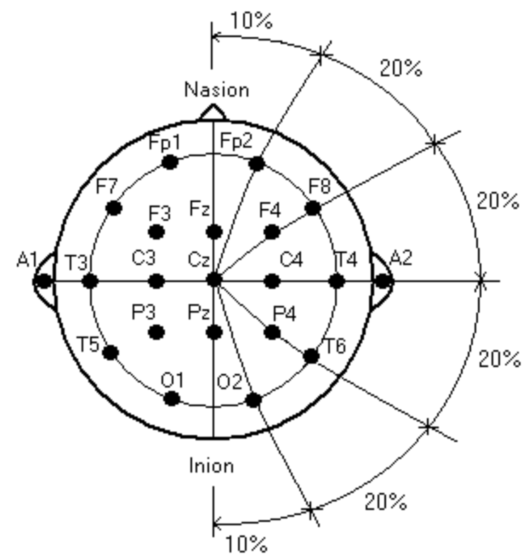

**Clinical Presentation:**

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

# Analysis of Electroencephalogram (EEG) Data




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

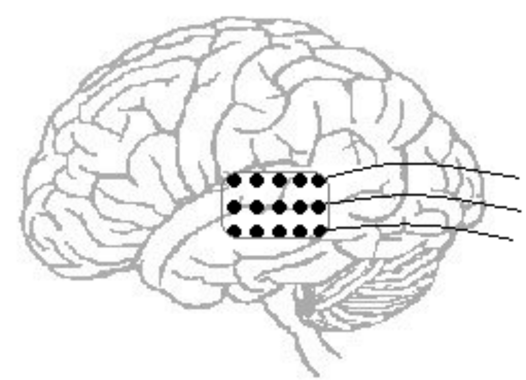



*Flowchart: Review of methods available for EEG analysis*

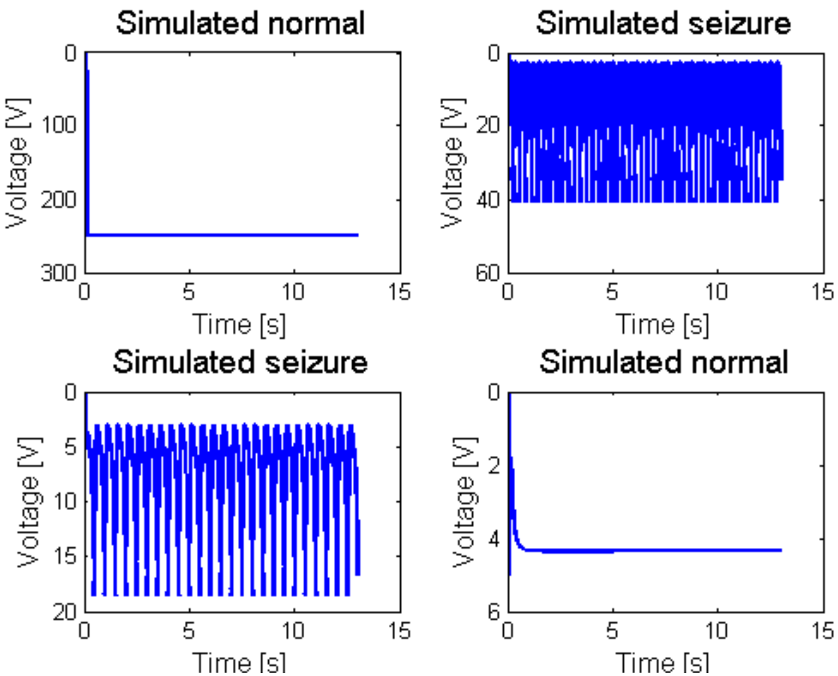
*<u>On Right:</u>*

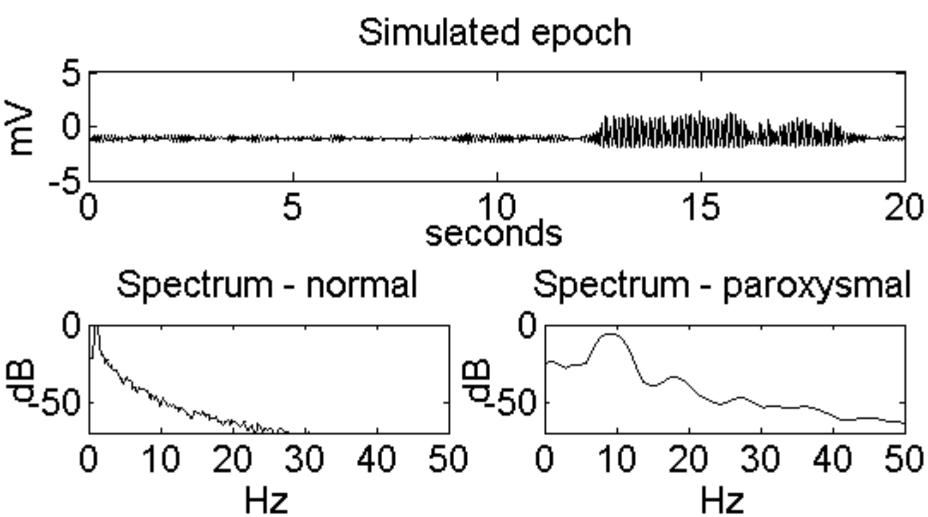
*Top: Scalp EEG data*

*Bottom: Intracranial grid EEG data*



# Models of Epilepsy: Animal and Computational




# Animal Models of Epilepsy

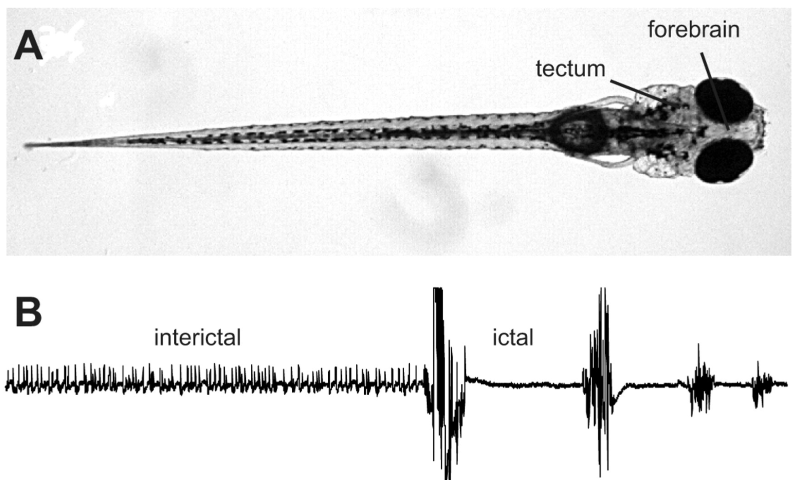
| **Species** | ***Drosophila melanogaster (fruit fly)*** | ***Danio rerio (zebra fish)*** | ***Mus musculus (mouse)*** | ***Canis familiaris (dog)*** | ***Papio hamadryas (baboon)*** |
|---|---|---|---|---|---|
| First epilepsy studies | Dynamin mutant | Pentylene-tetrazole | Audio-genic | Electro convulsive | 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:**

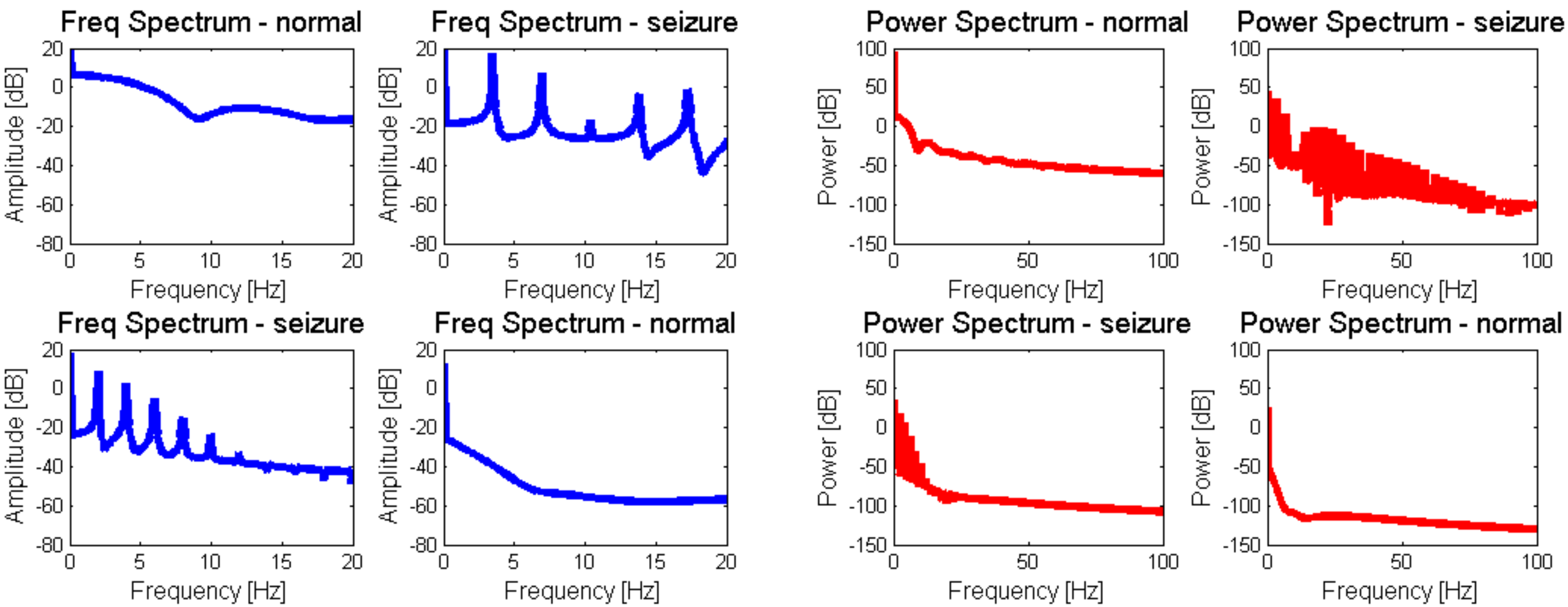
- Knockdown of genes
- SCN1A Mutants

**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**

# Schizophrenia

**Definition**: a chronic and severe mental disorder that affects how a person thinks, feels and behaves.

**Signs and symptoms:**

- Visible between ages 16 and 30
- Three categories: positive, negative and cognitive
  - Positive: overt symptoms that should not be present
  - Negative: lack of characteristics that should be present
  - Cognitive: cognitive deficits that make it hard to live a normal life

# Schizophrenia

## **Examples of symptoms**:

**Positive –** people “lose touch” with some aspects of reality

- Hallucinations
- Delusions
- Thought disorders (unusual or dysfunctional ways of thinking)
- Movement disorders (agitated body movements)

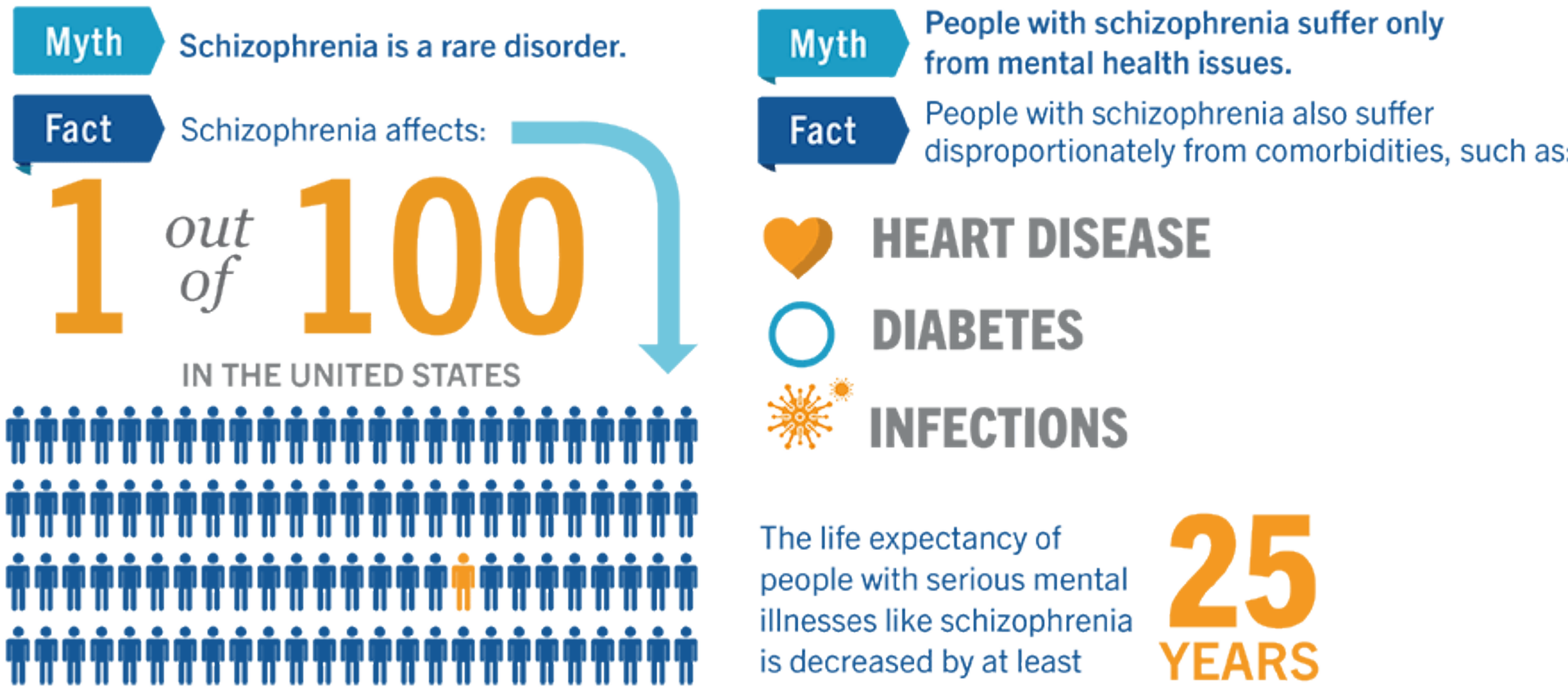
**Negative** –

- “Flat effect” (reduced expression of emotions via facial expression or voice tone)
- Reduced feelings of pleasure in everyday life
- Difficulty beginning and sustaining activities
- Reduced speaking

**Cognitive** –

- Poor “executive functioning” (the ability to understand information and use it to make decisions)
- Trouble focusing or paying attention
- Problems with “working memory” (the ability to use information immediately after learning it

# Misconceptions about schizophrenia

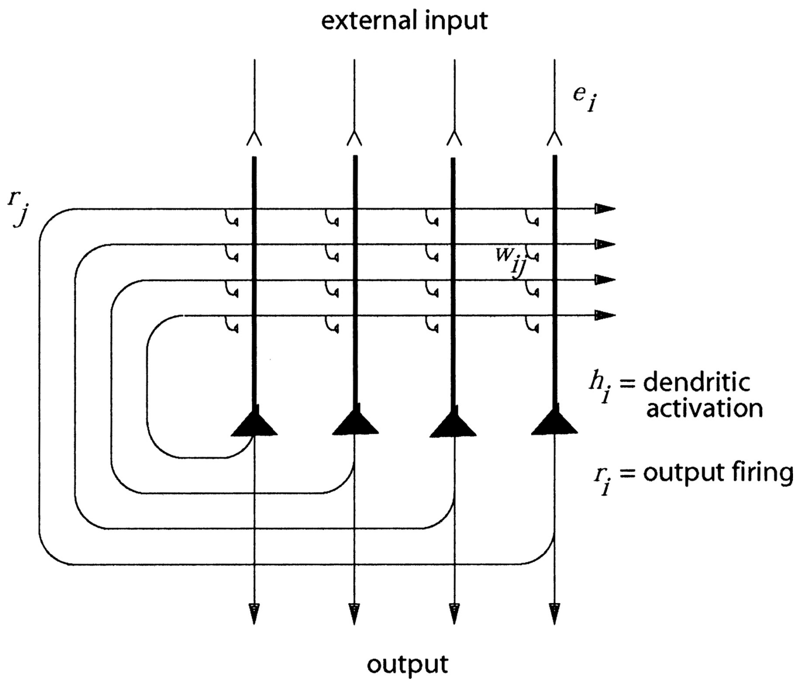



A lot of the research being done about schizophrenia focuses on combating the positive symptoms. This happens because these unsettling manifestations of the disease are disturbing – this does result in fewer treatment options for negative symptoms.

# Computational models of schizophrenia

**Difficulties with designing a model**: the disease is complex and heterogeneous

Models involving **neural networks** have begun to address how this disorder has divergent symptoms.




## Why use neural networks?

- Models that include neurons with ion channels can model the effects of synaptic currents (i.e. integrate-and-fire)
- Researchers can investigate the effects of alterations in ion channels on the entire neural network, in order to:
  - Maintain a short-term memory
  - Maintain attention and initiate action
  - Decision making

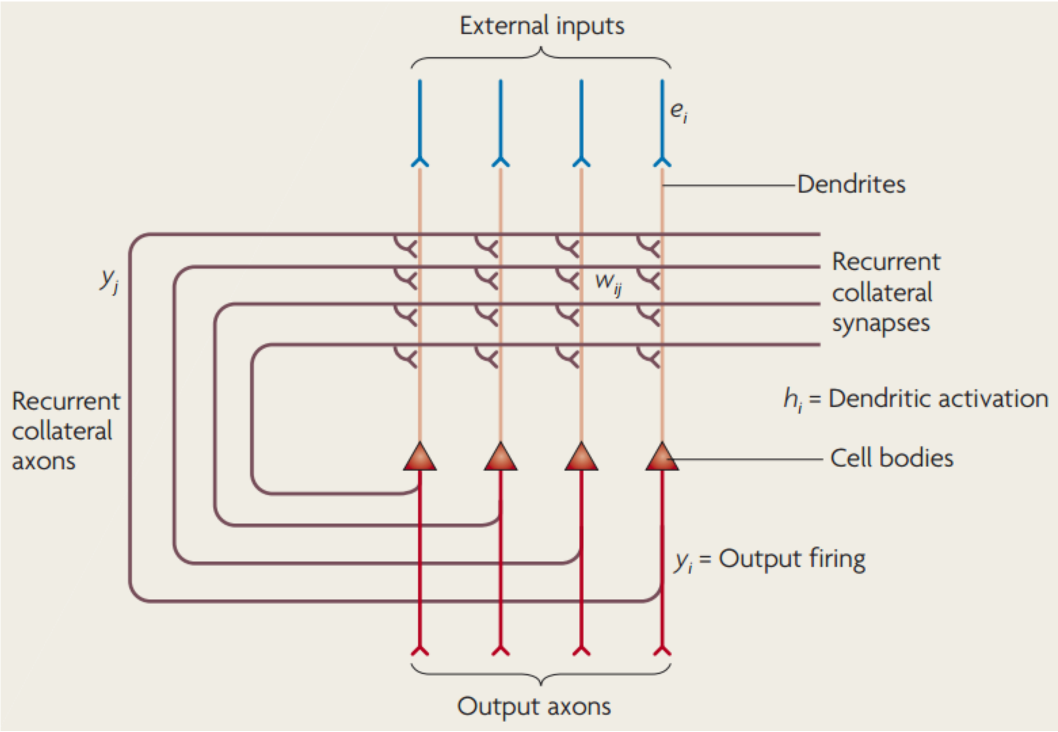
# Attractor networks to model schizophrenia

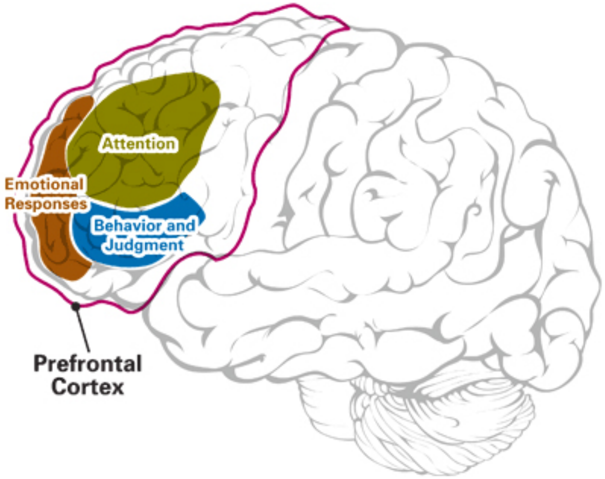
Used to model cognitive symptoms of the disorder.

**Attractor networks** are important for short-term memory and attention and the random firing of neurons can influence the stability of these networks by introducing stochastic noise.

An **attractor network** is a network of neurons with excitatory connections that can settle into a stable pattern of firing.

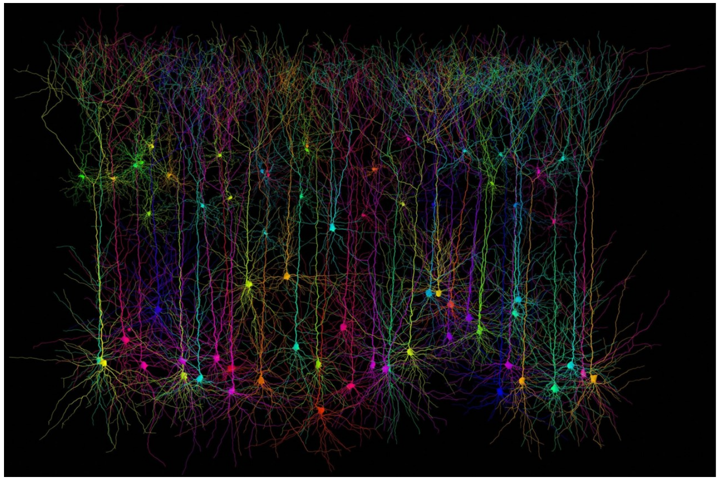
Attractor networks operate in the prefrontal cortex and can contribute to short-term memory and attention.



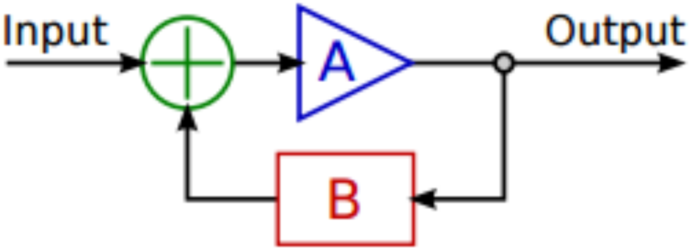



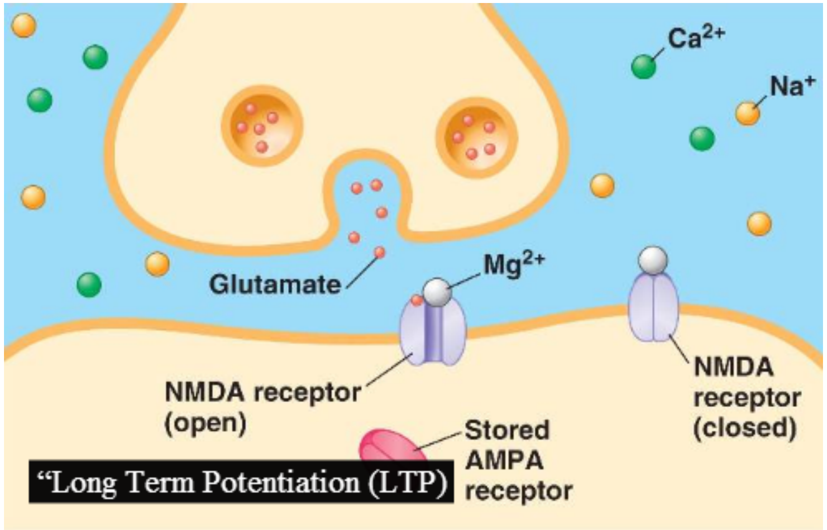
# Biological motivation for attractor network

Pyramidal neurons in the cerebral cortex have a high density of excitatory connections to each other.



Local recurrent excitatory connections provide a positive-feedback mechanism (controlled by GABA) that allows a set of neurons to maintain their activity for a few seconds so a short-term memory can be formed.



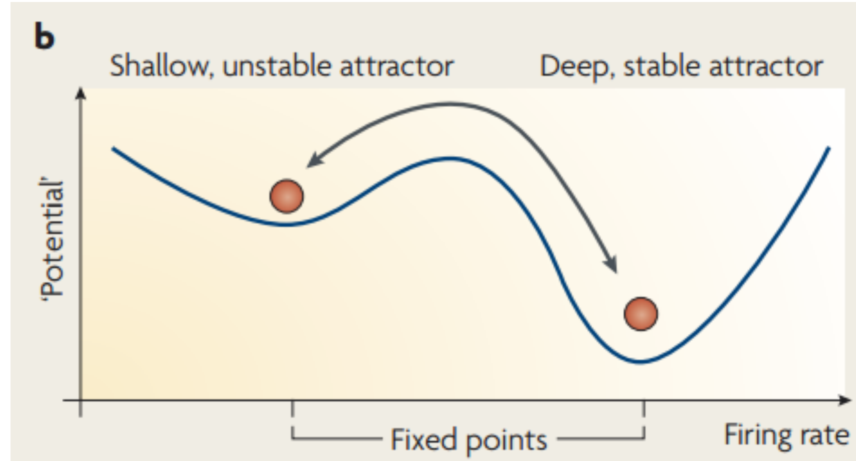



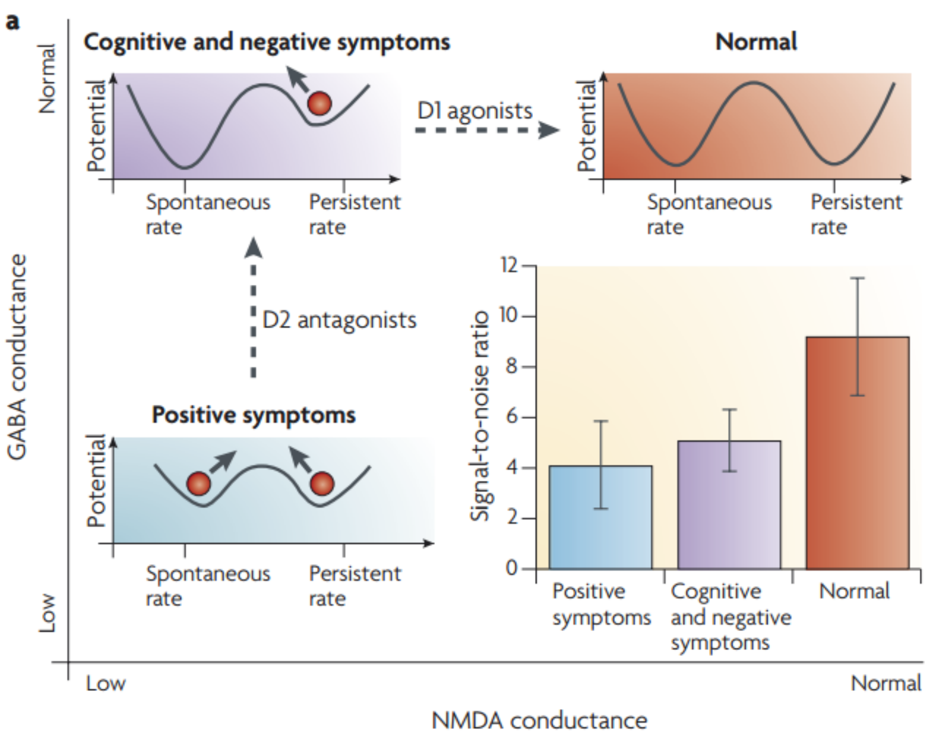

Forming a memory involves strengthening the excitatory connections between that set of neurons (**long-term potentiation**).

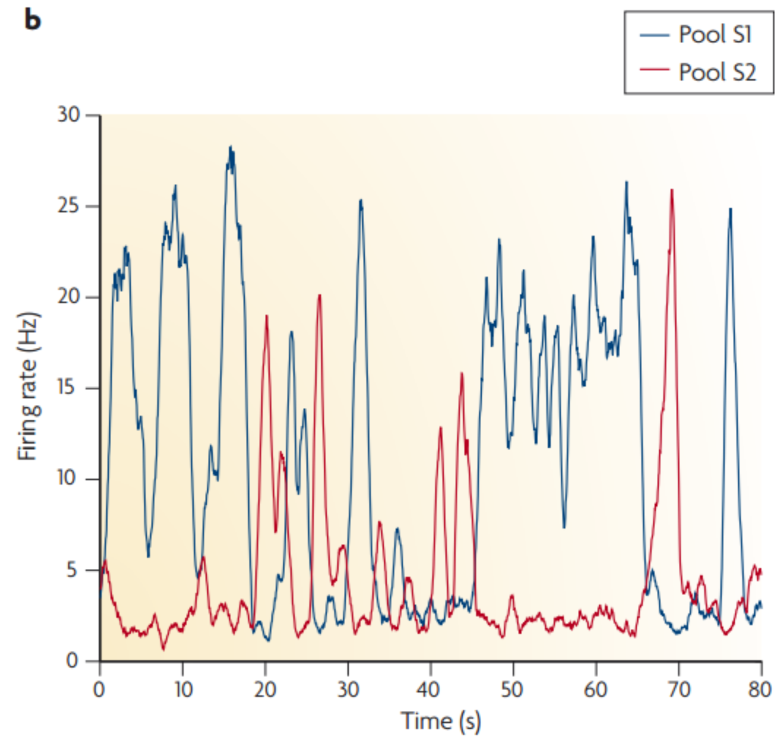
# Attractor network stability

Two types of stable, fixed points:
**Spontaneous state** – has a low firing rate
**Persistent state** – high firing rate, where neurons keep firing

Each of these states can implement a different memory.



# Animal models of schizophrenia

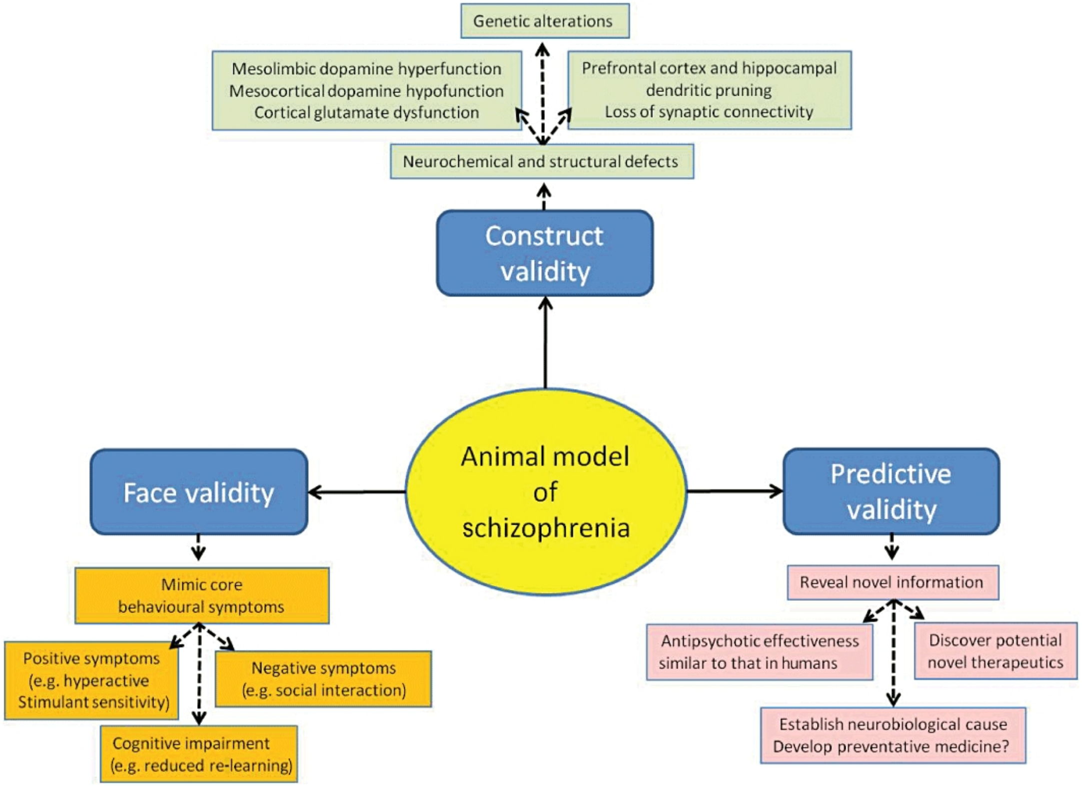
Different types of models:

**Pharmacologic:** good construct validity, bad face validity, okay predictive validity

- Dopamine
- Glutamate
- Serotonin
- GABA

**Lesion**

- Neonatal lesion



# Congratulations!