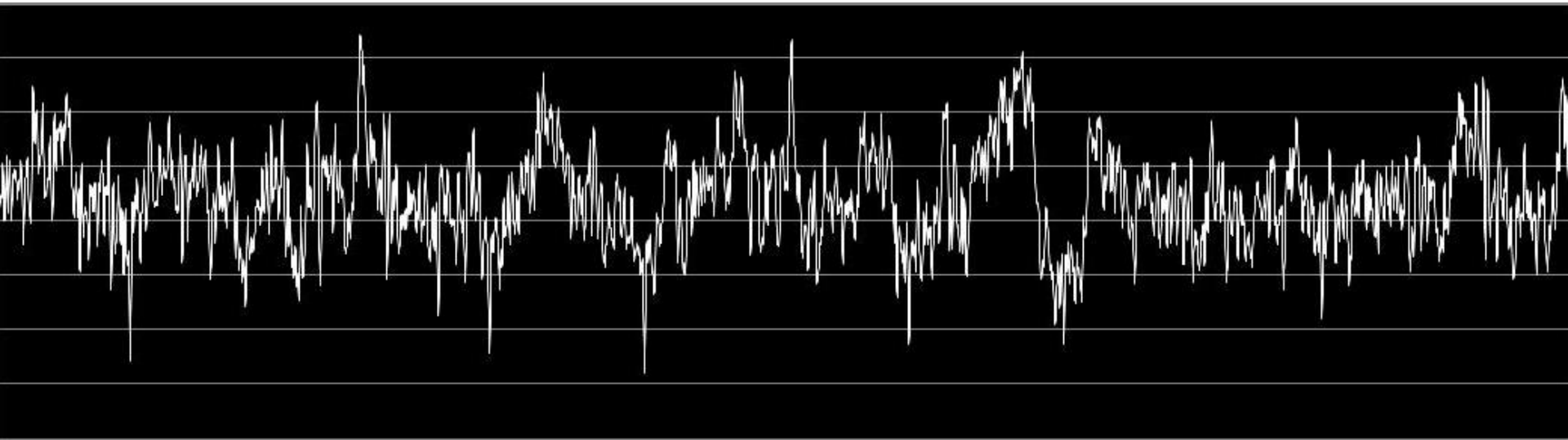
Applied Neuroscience

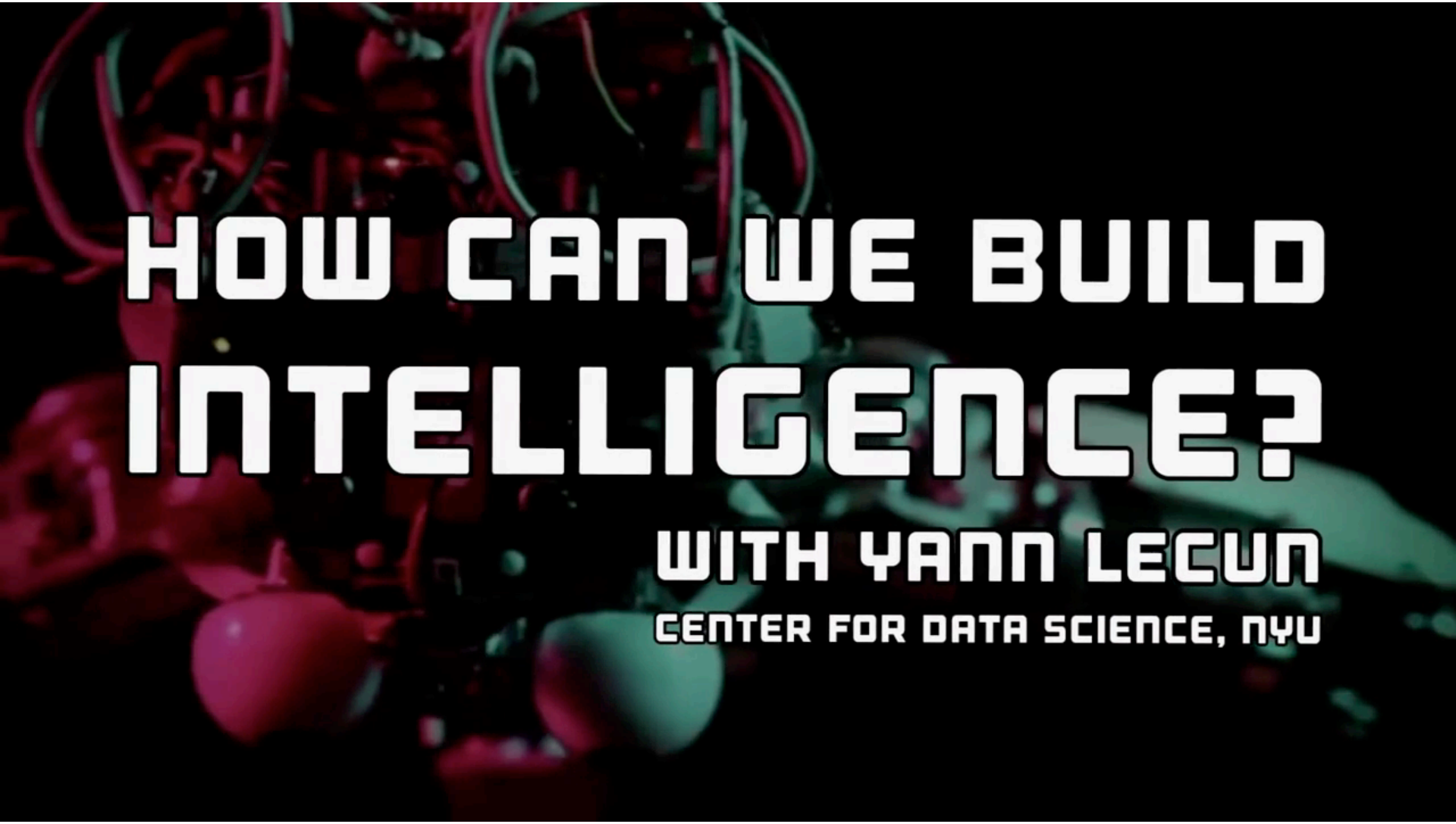
Columbia Science Honors Program

Spring 2017

Computational Models of Psychiatric Disorders



Artificial Intelligence

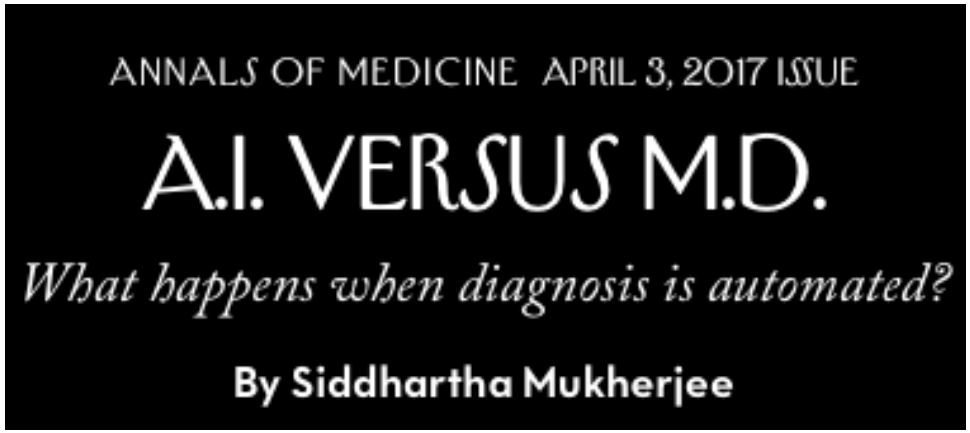


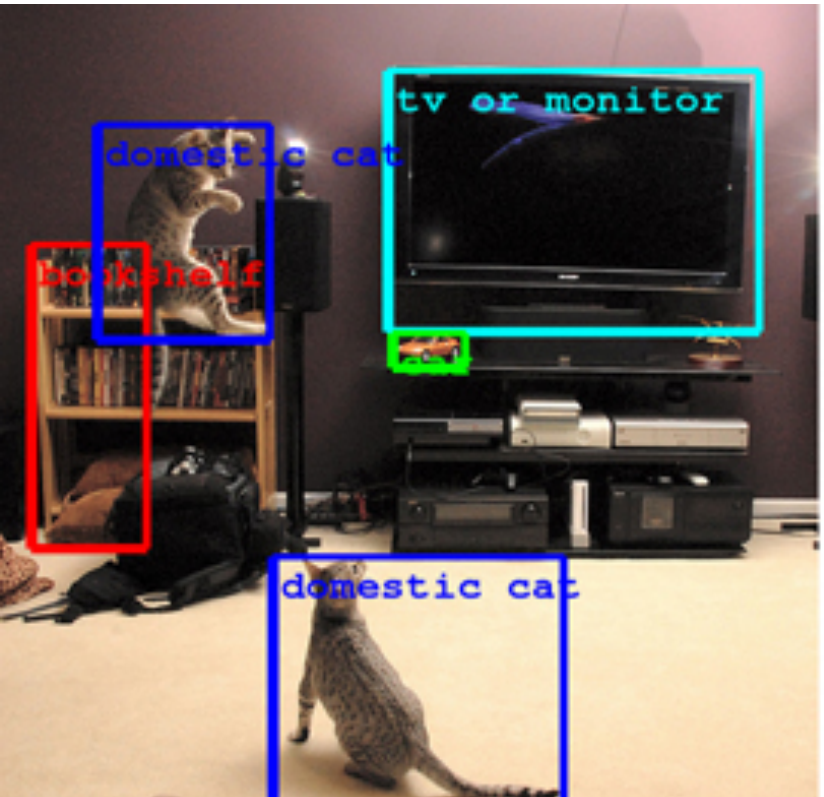
Artificial Intelligence

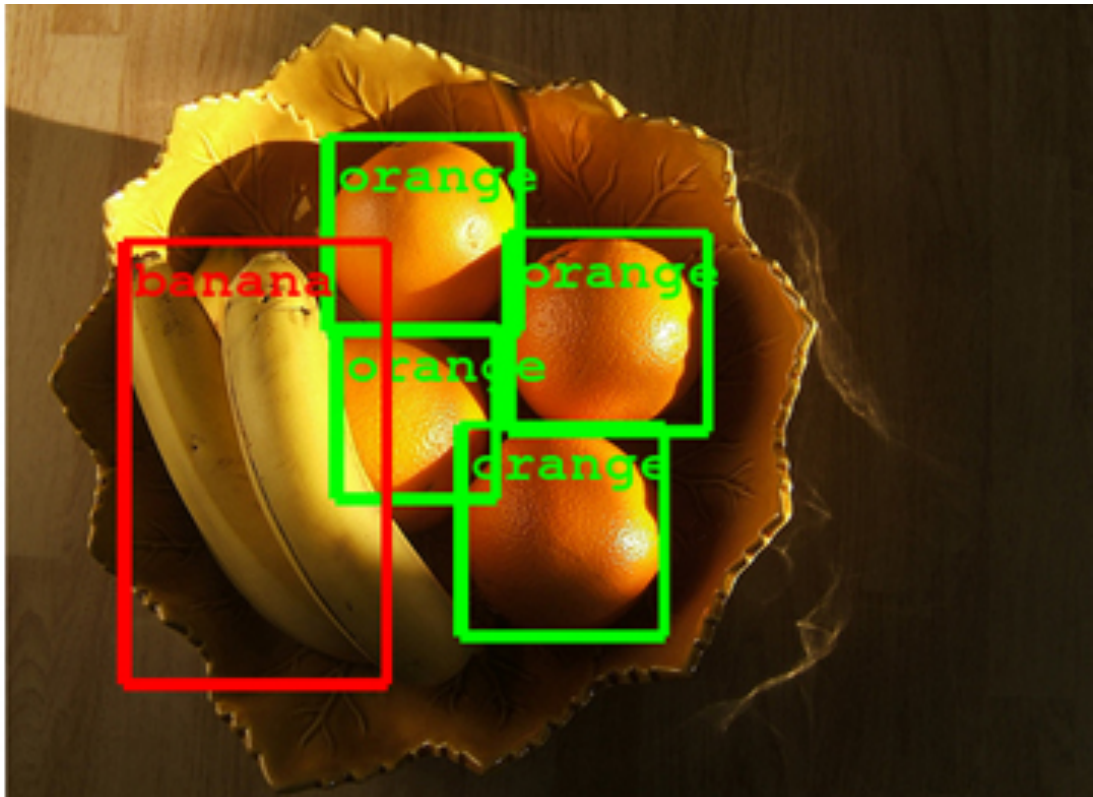
Applications in the near future:

1. Self-Driving Cars
2. Medical Diagnosis

Geoffrey Hinton aims to use deep learning algorithms to read X-rays, CT scans, and MRIs of every variety.





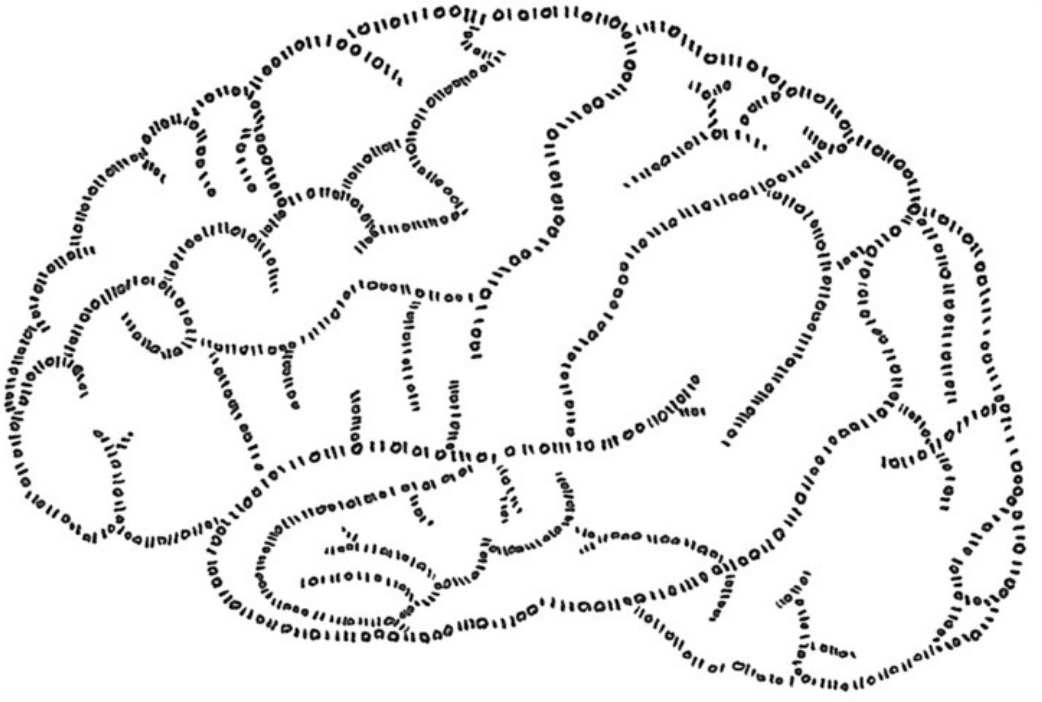


Psychiatric Disorders

Objective: Role of Computational Models in Psychiatry

Agenda:

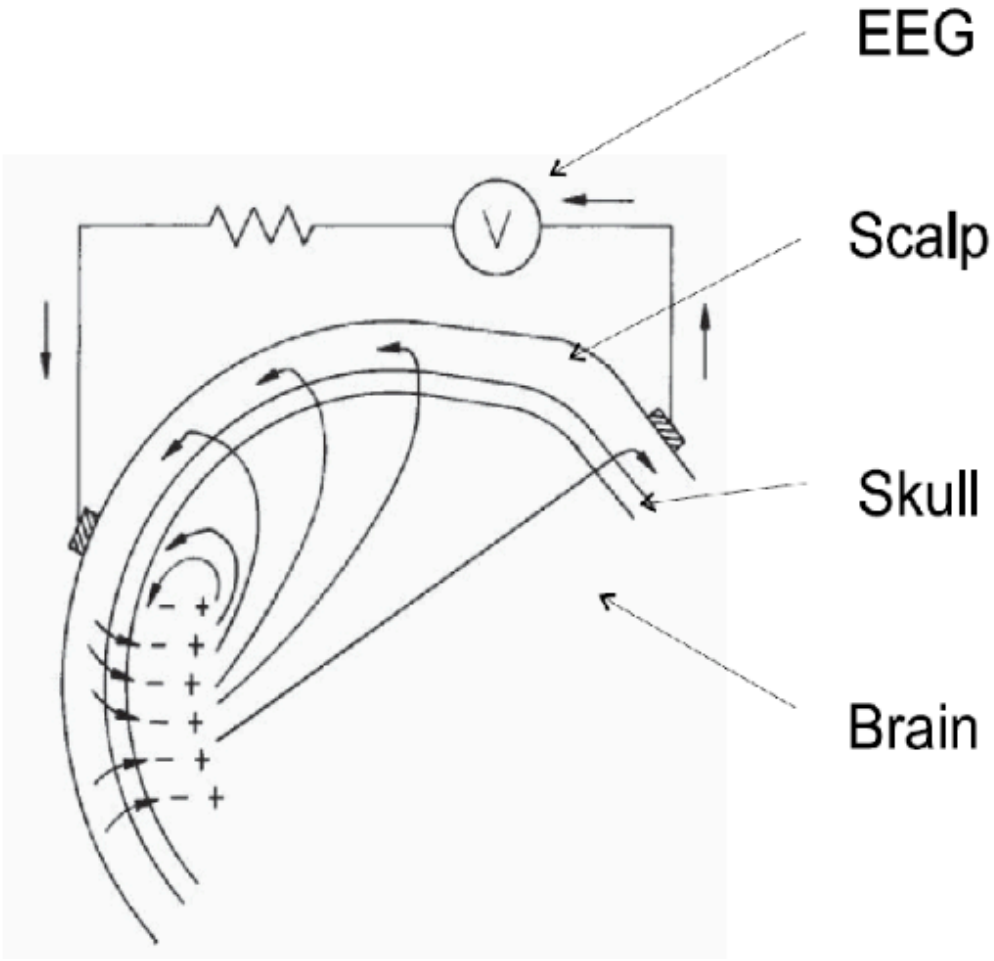
1. Neural Imaging
   - *EEG*
   - *fMRI*
2. Psychiatric Disorders
   - *Schizophrenia*
3. Seizure Prediction
   - *Epilepsy*

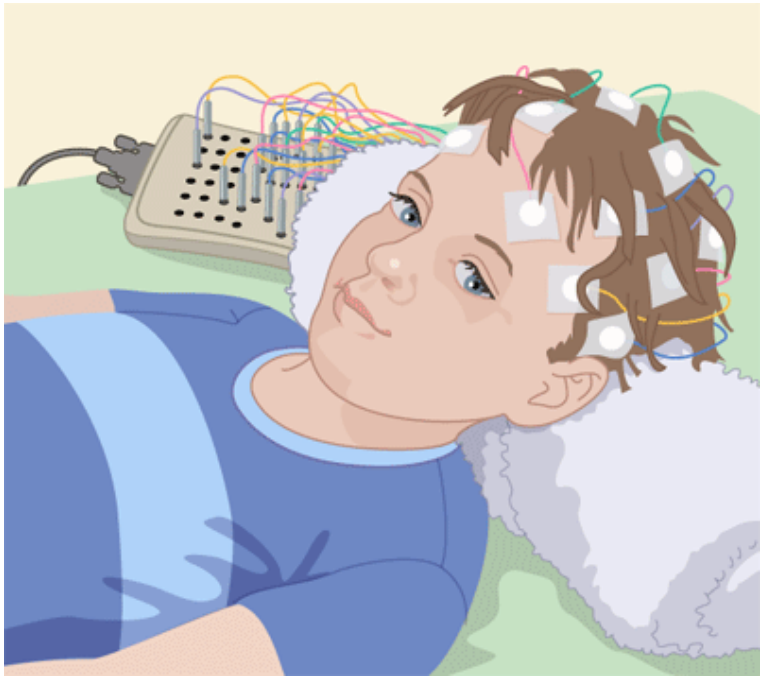


Classification of Patterns of EEG Synchronization for Seizure Prediction

Piotr Mirowski MSc*, Deepak Madhavan MD†, Yann LeCun PhD*, Ruben Kuzniecky MD‡

Electroenchaplography (EEG)



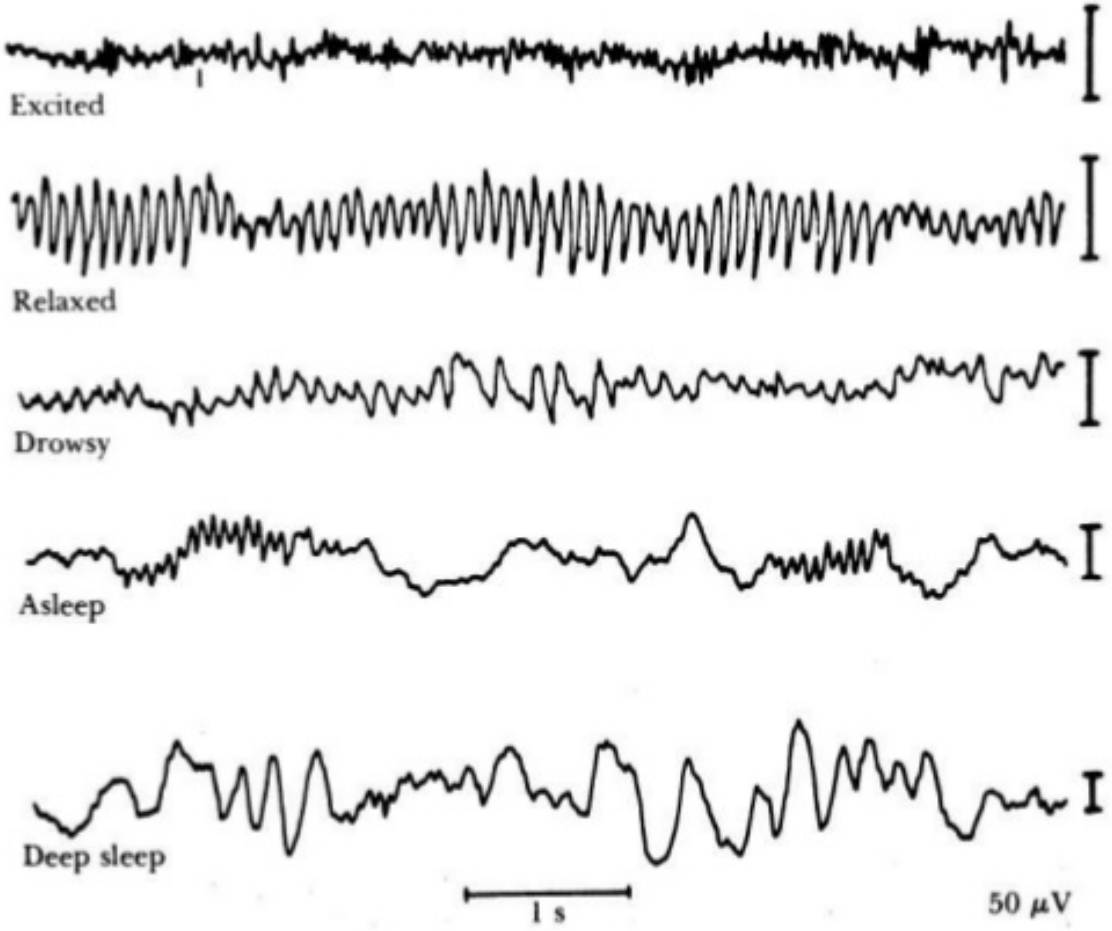


Current in the EEG measuring circuit depends on the nature and location of the current sources, on the electrical properties of the brain, skull and scalp and on location of both electrodes. *Source: Nunez et al (1891)*

Electroenchaplography (EEG)

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

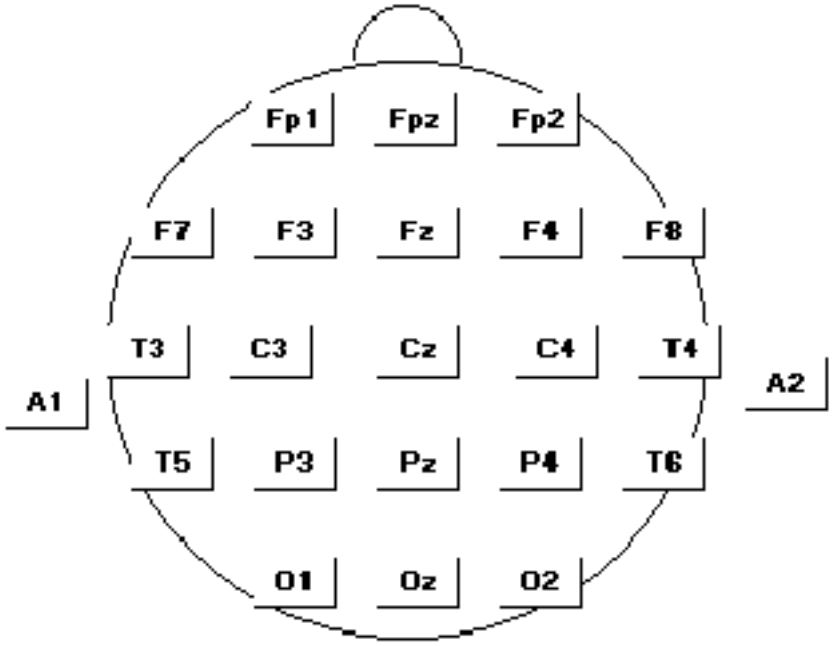
- Often non-invasive
- Measures voltage fluctuations resulting from ionic current within neurons
- Used to diagnose epilepsy
- Limited spatial resolution
- Temporal resolution at millisecond scale



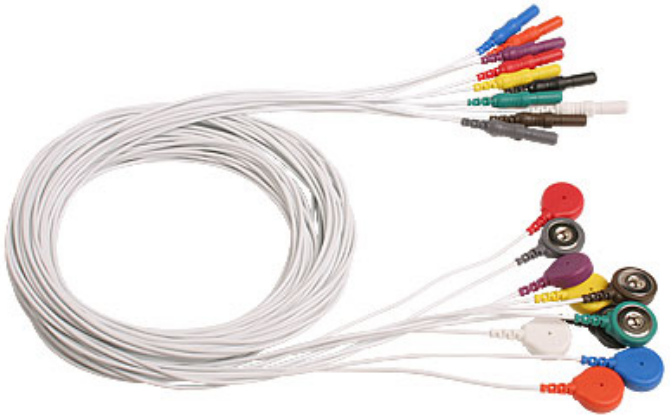
Electrodes

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

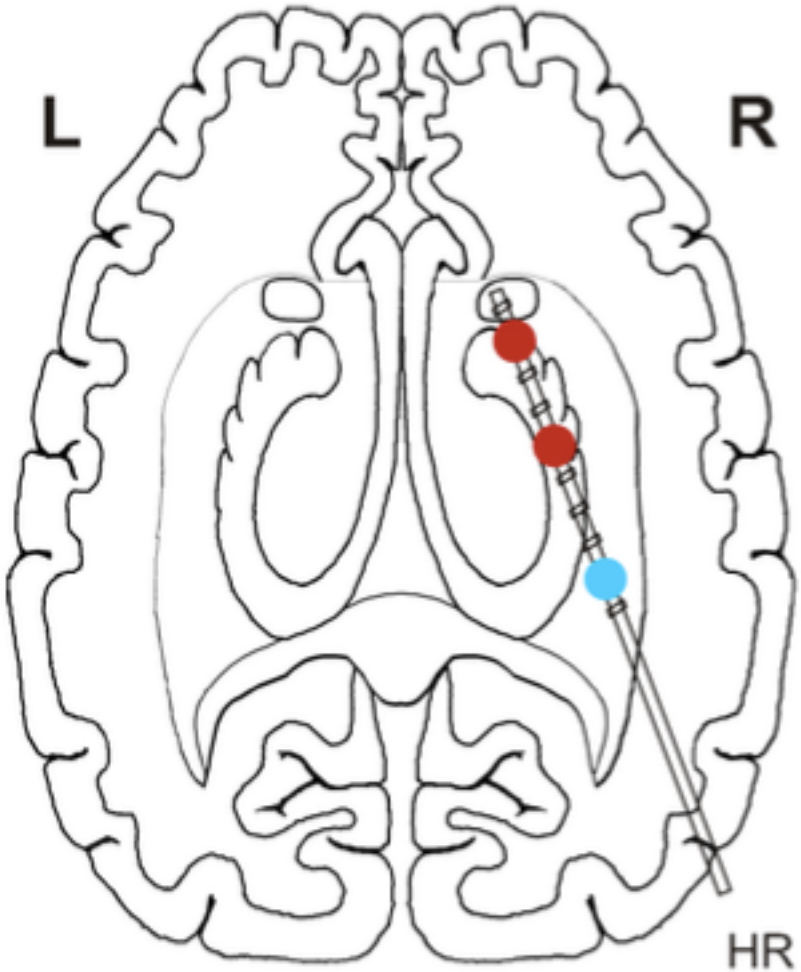
- Each electrode site is labeled with a letter and a number
- Letter: F is frontal lobe and T is temporal lobe
- Number: Even number means right side of head and odd number means left side of head
- Can be made of: stainless steel, tin, gold or silver covered with a silver chloride coating



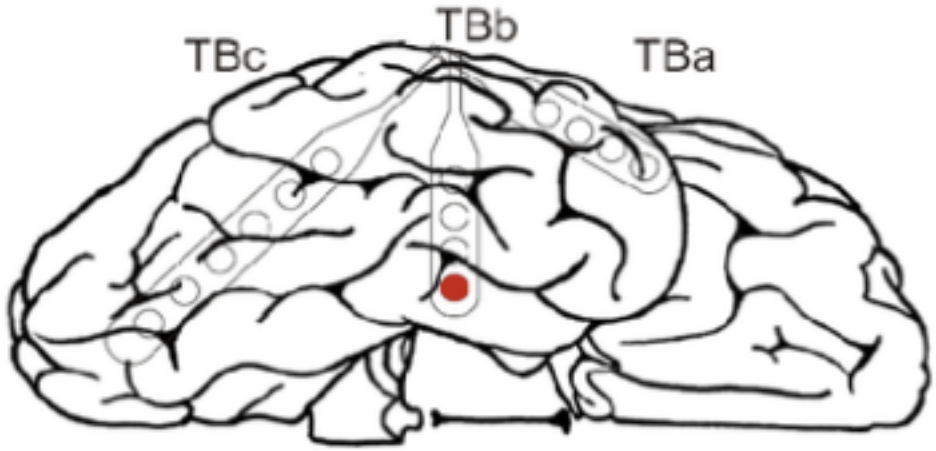
10/20 System of electrode placement



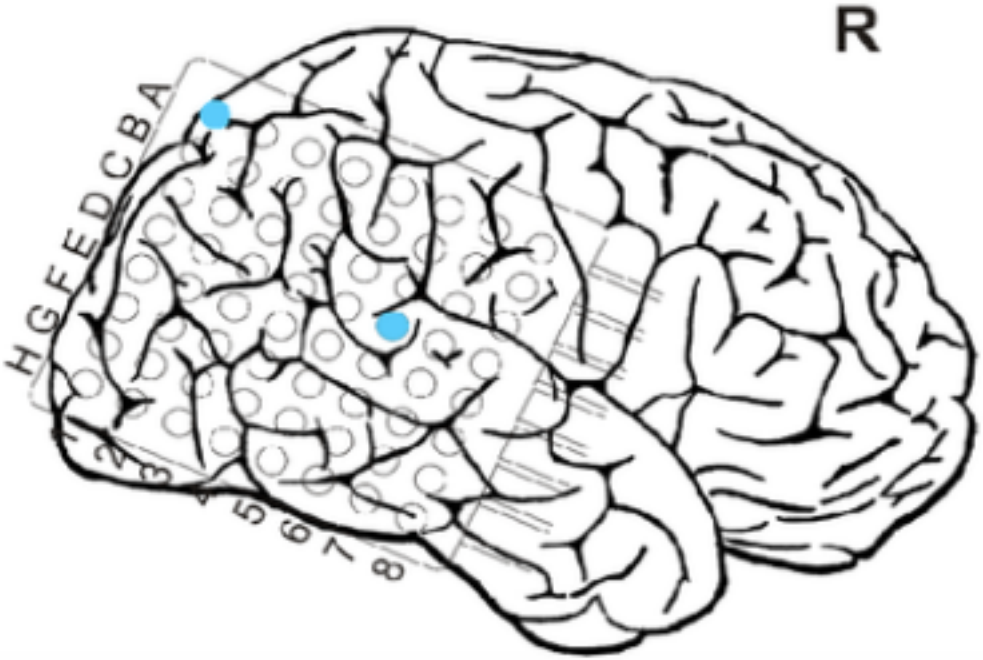
Intra(cranial/cerebral) EEG



Depth electrodes



Strip electrodes



Grid electrodes

Test Your Understanding:

1. 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

2. Assume two neurons are connected by an electrical synapse. What would happen if two neurons located at opposite ends were electrically stimulated at their axons simultaneously?
    A. Action potentials would pass in the middle and travel to opposite ends
    B. Action potentials would meet in the middle and be propagated back to their starting site
    C. Action potentials would meet in the middle and stop there

Test Your Understanding:

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

    <u>Explanation:</u> 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.

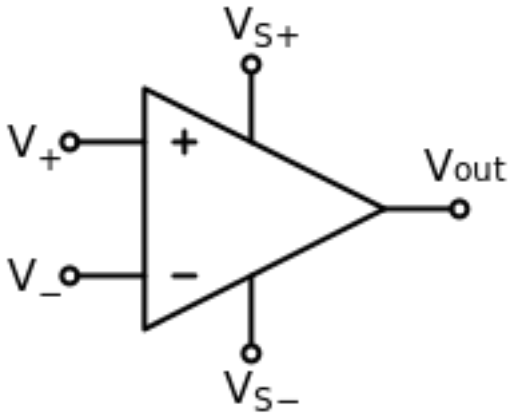
Test Your Understanding:

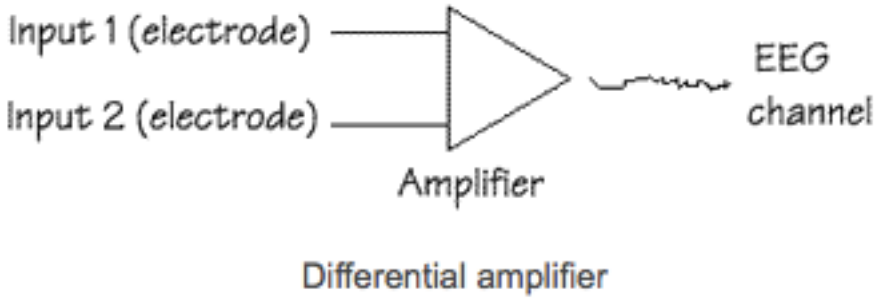
2. Assume two neurons are connected by an electrical synapse. What would happen if two neurons located at opposite ends were electrically stimulated at their axons simultaneously?
    A. Action potentials would pass in the middle and travel to opposite ends
    B. Action potentials would meet in the middle and be propagated back to their starting site
    C. Action potentials would meet in the middle and stop there

<u>Explanation:</u>
*Action potentials are generated by the axons of both neurons at the same time and travel in opposite directions. The movement of an action potential is **unidirectional.** When the two action potentials moving towards each other meet in the middle, both neurons will be in the refractory period. Thus, the action potentials cannot be propagated in either direction.*

Introduction to EEG

EEG machines use a **differential amplifier** to produce each channel or trace of activity. Each amplifier has two inputs and an electrode is connected to each of the inputs:





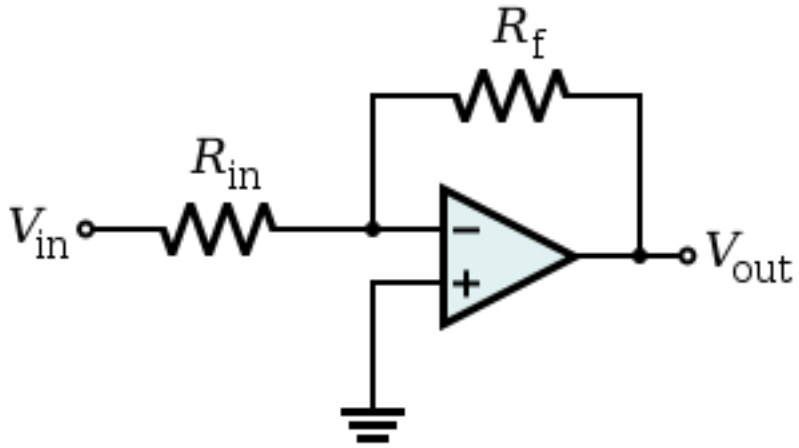
Differential amplifier

A differential amplifier is the combination of inverting and non inverting amplifier:

- Amplifies the difference between two input voltages
- Suppresses any voltage common to the two inputs
- A is the gain of the amplifier

$$V_{out} = A(V_{in}^{+} - V_{in}^{-})$$

Inverting Amplifier



Derivation of Gain:

1. Calculate current in R_{in}:

$$i_{in} = \frac{V_{in}}{R_{in}}$$

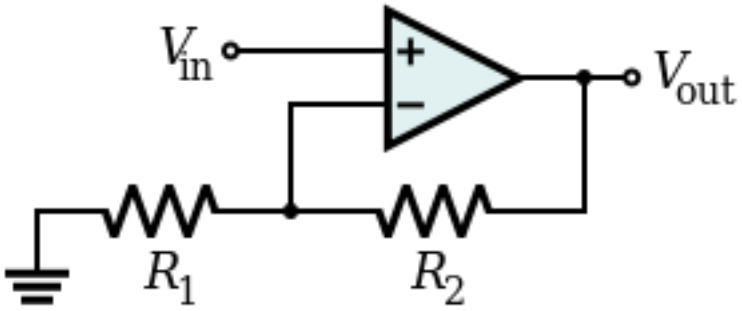
2. Given:

$$V_- = V_+ = 0$$

3. As the same current in R_{in} passes through R_f, calculate V_{out}:

$$V_{out} = -i_{in} R_f = -V_{in} \frac{R_f}{R_{in}}$$

Non-Inverting Amplifier



Derivation of Gain:

1. Calculate current in R_1:

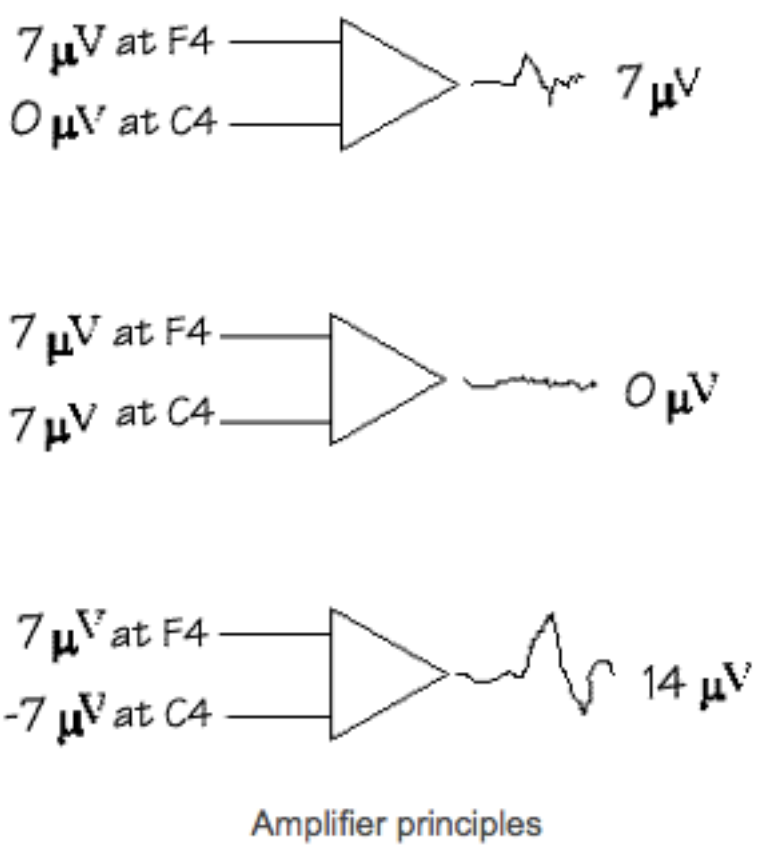
$$i_1 = \frac{V_{in}}{R_1}$$

2. As the same current in R_1 passes through R_2, calculate V_{out}:

$$V_{out} = V_{in} + i_i R_2 = V_{in}(1 + \frac{R_2}{R_1})$$

Differential Amplifiers

$$V_{out} = V_2 - V_1$$



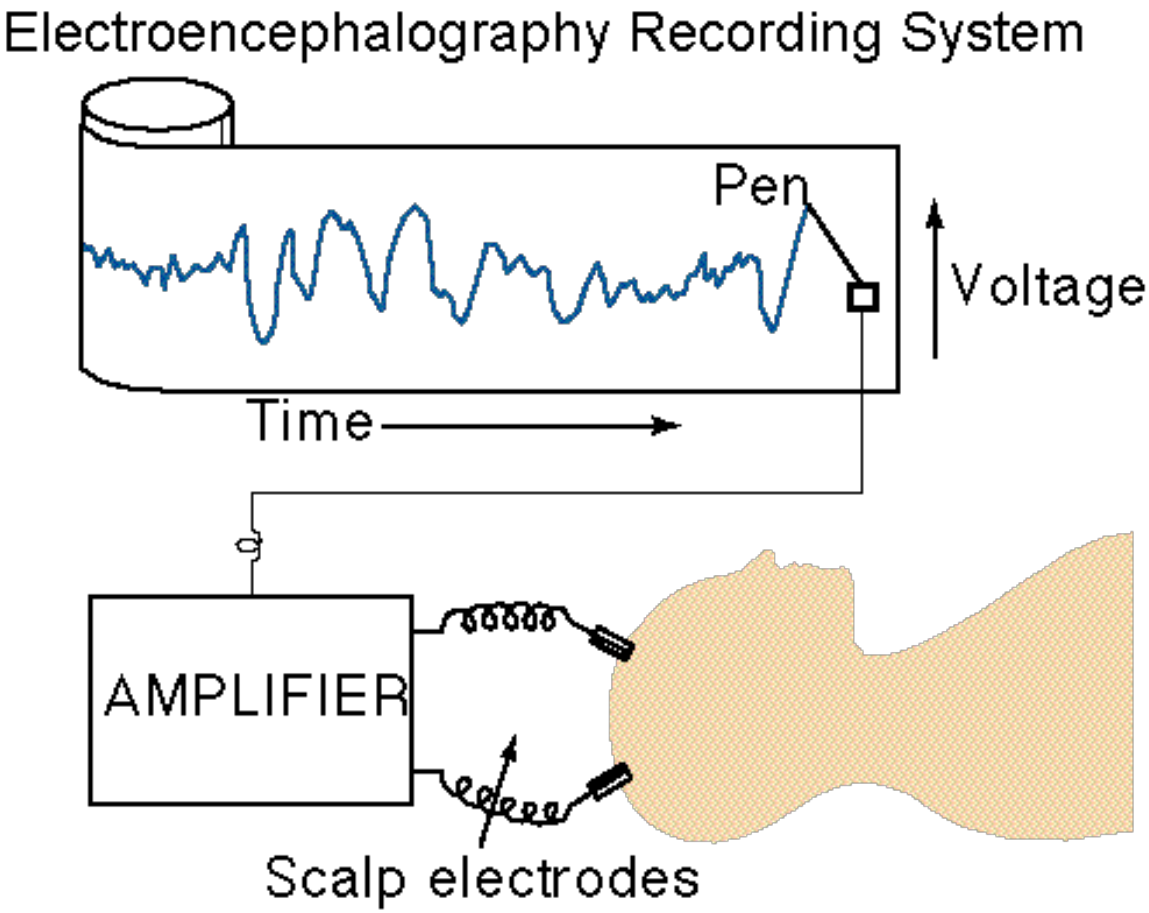
Amplifier principles

Differential amplifiers measure the voltage difference between two signals at each of its inputs. The resulting signal is amplified and then displayed as a channel of EEG activity.

Montage: the manner in which pairs of electrodes are connected to each amplifier of the EEG machine

1. Common reference
2. Average reference
3. Bipolar

EEG Instrumentation



Analog EEG instruments use an amplifier, galvanometer and a writing device.

The output signal from the amplifier passes through the wire causing the coil to oscillate. A pen mounted on the galvanometer moves up and down each time the coil moves. The pen draws the trace onto paper moving below it.

The amplifier output is controlled by high and low frequency filters (**bandwidth**) and sensitivity controls (affects size of activity displayed). A digital EEG system converts the waveform into numerical values.

EEG Monitoring

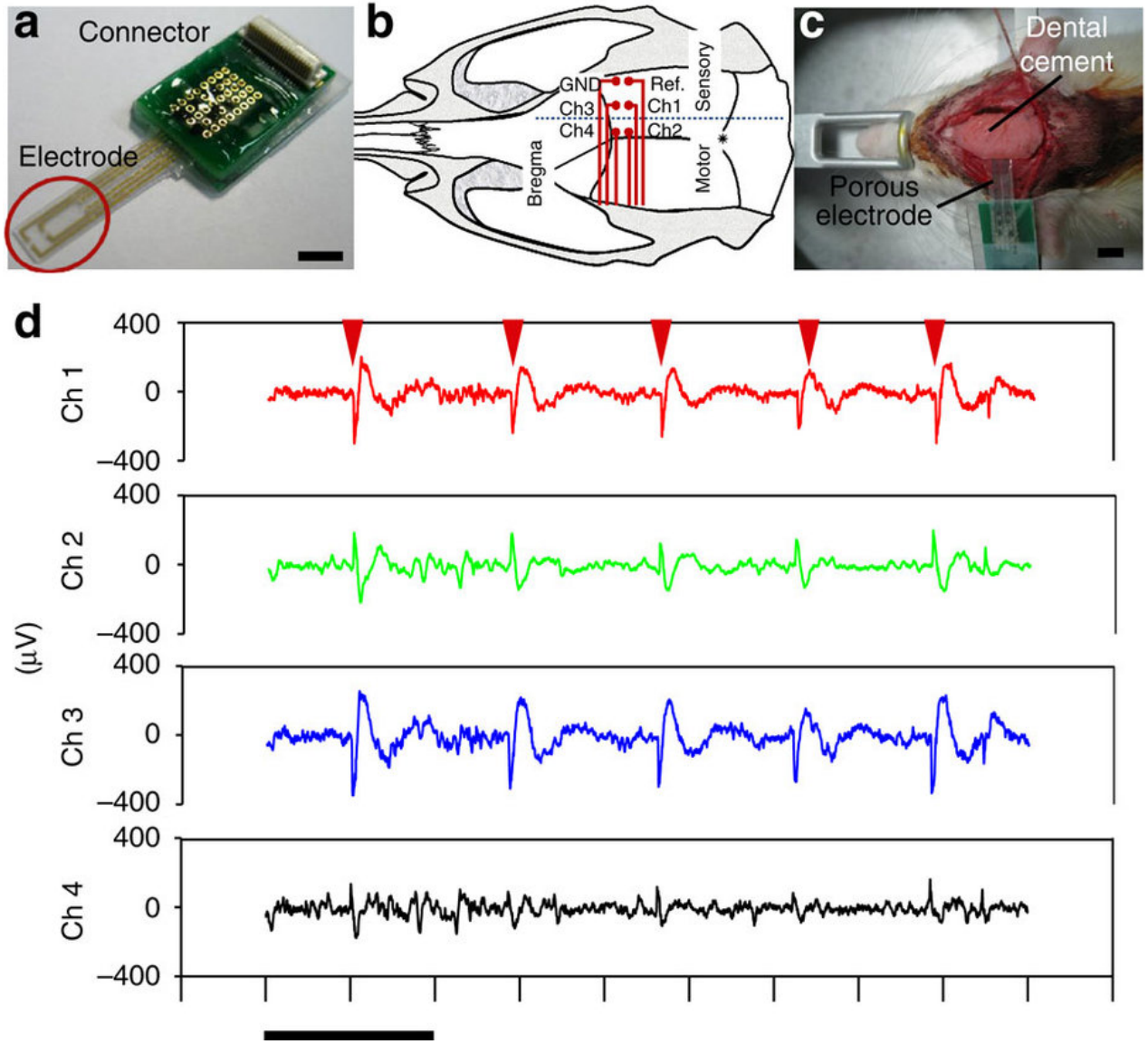
There are two ways to do recordings:

1. **Extracellular recording:** electrode outside neuron
2. **Intracellular recording:** electrode inside neuron

Paired Recording: technique in which one inserts electrodes into pre-synaptic neuron and post-synaptic neuron simultaneously

1. Inject de-polarizing current to activate pre-synaptic neuron.
2. Observe effect on post-synaptic neuron:
    - Excitatory synapse results in EPSP
    - Inhibitory synapse results in IPSP

EEG Monitoring



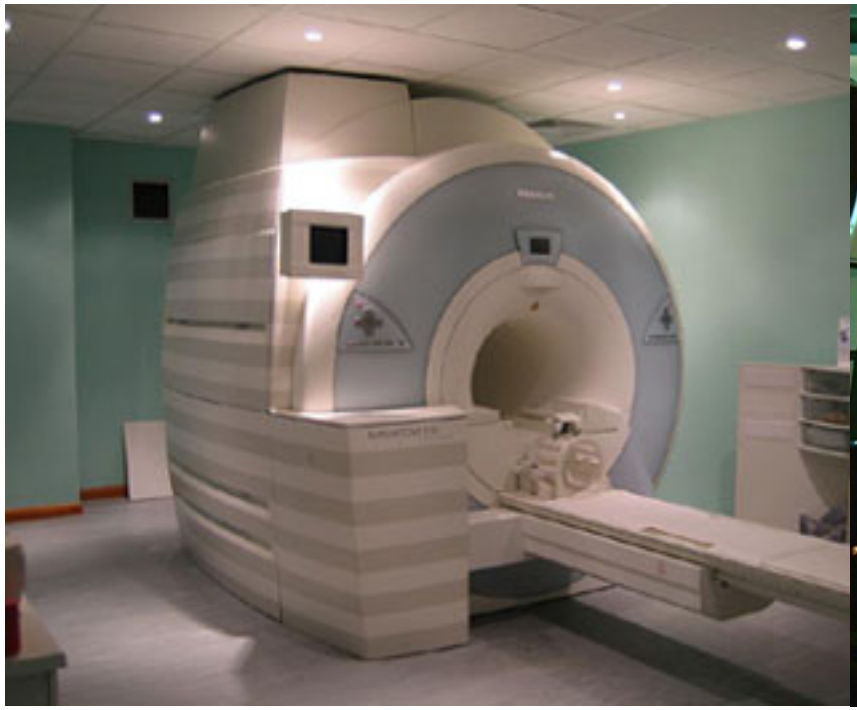
a. Electrode used to measure evoked potential signal from the skull of a rat

b. Location of electrode array

c. Electrode mounted and fixed with dental cement

d. Electrode recordings of voltage over time

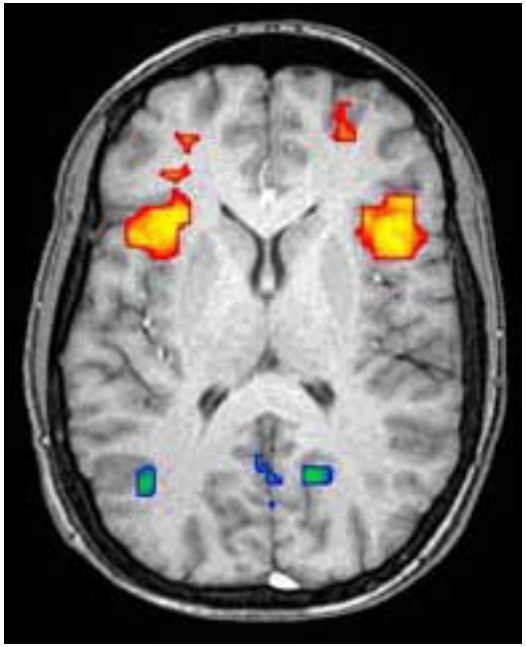
Functional Magnetic Resonance Imaging



Functional MRI measures brain activity by detecting associated changes in blood flow. The primary form of fMRI uses blood-oxygen-level-dependent (**BOLD**) contrast, discovered by Seiji Ogawa.

When nerve cells are active, they consume more oxygen and switch to less energetically effective, but more rapid anaerobic glycolysis. This local response to oxygen utilization increases blood flow to regions of increased neural activity.

Functional Magnetic Resonance Imaging



<u>On left:</u> Axial MRI slice at the level of the basal ganglia, showing fMRI BOLD signal changes overlaid in red (increase) and blue (decrease) tones.
Note that neurons lack internal energy reserves in the form of glucose and oxygen, which is required for firing.

Physicians perform functional MRI to:

- Examine the anatomy of the brain
- Brain mapping
- Assess effects of stroke, trauma or degenerative disease (such as Alzheimer's) on brain function
- Monitor growth and function of brain tumors
- Guide planning of surgery and radiation therapy

Neurobiology of Psychiatric Illness:

Review of functional neuroanatomy

Schizophrenia

Psychiatric Disorders

1. Psychiatric illnesses are diagnosed by symptom clusters that are the result of abnormal brain tissue, or activity in specialized areas of the brain.

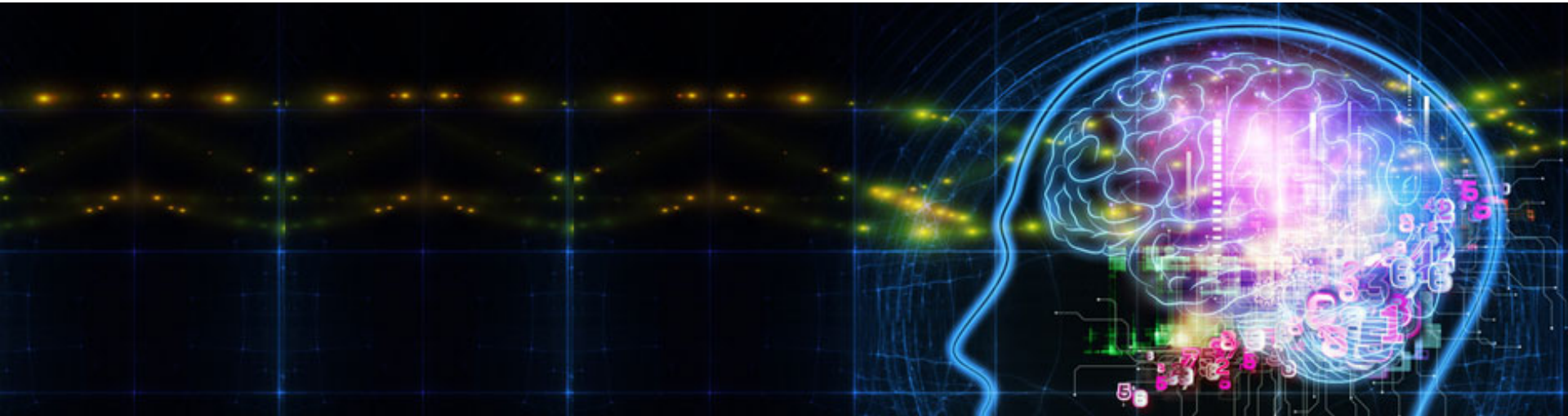
2. Dysregulated circuitry results from abnormal neural function, or abnormal neural connections from one brain area to another.

3. Symptoms in psychiatric illnesses are the consequence of dysregulated neurocircuitry.

Neurocircuitry Dysfunction

Each psychiatric illness has uniquely dysregulated circuitry. Commonly implicated neural circuits in psychiatric disorders include:

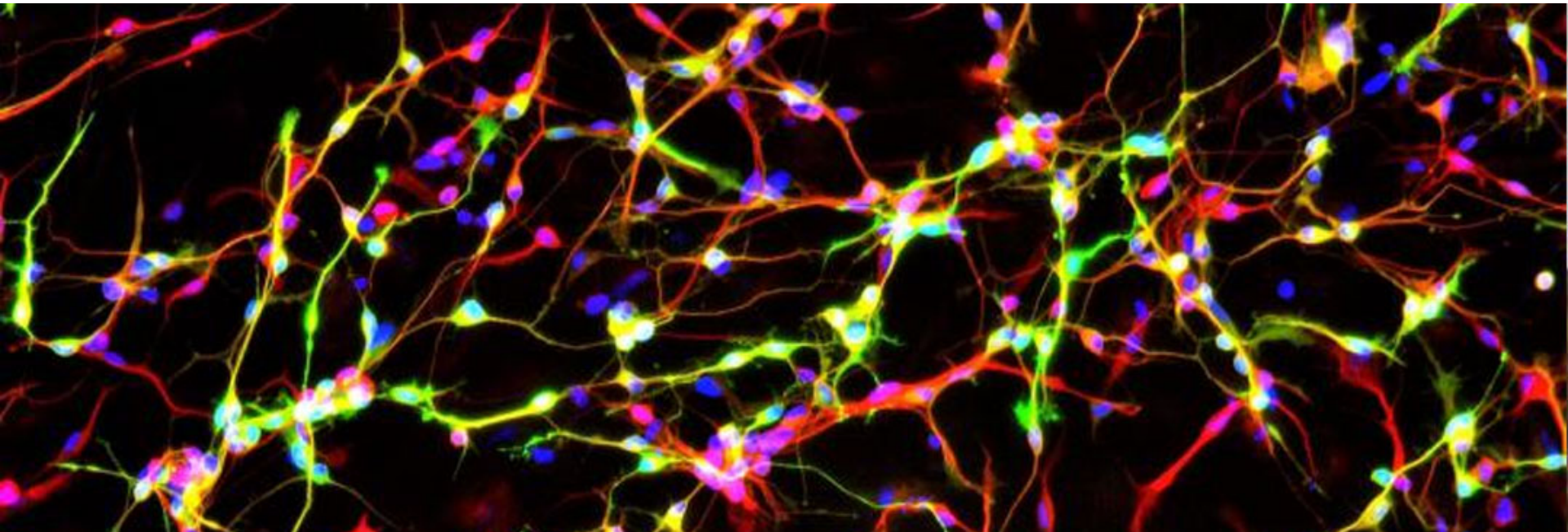
1. Prefrontal cortical-striatal-pallidal-thalamic pathways
2. Prefrontal cortical-limbic pathways
3. Prefrontal cortical-aminergic feedback pathways
4. Limbic circuits
5. Diffuse innervation by bio-genic amine nuclei in brainstem



Systems level dysregulation in psychiatric illness

Abnormal neuronal function in dysregulated circuits can be caused by changes in:

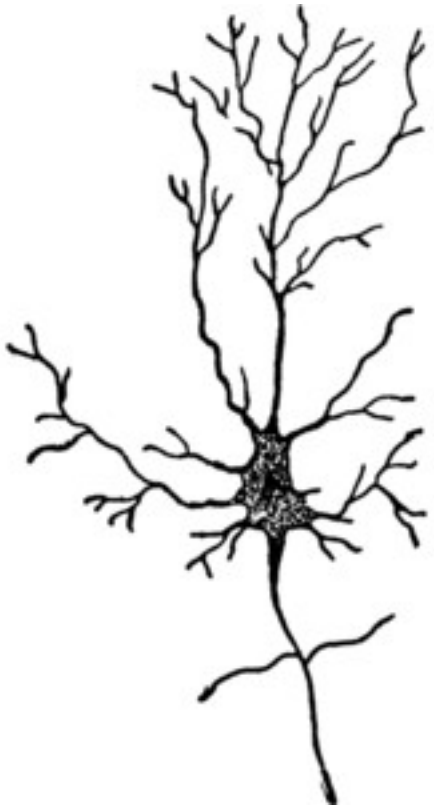
1. Number of neurons or neuropil (glia)
2. Density of connections between neurons
3. Receptor number or function
4. Neurotransmitter release
5. Proteins that transduce neurotransmission (i.e. receptors)
6. Second messenger systems
7. Gene expression



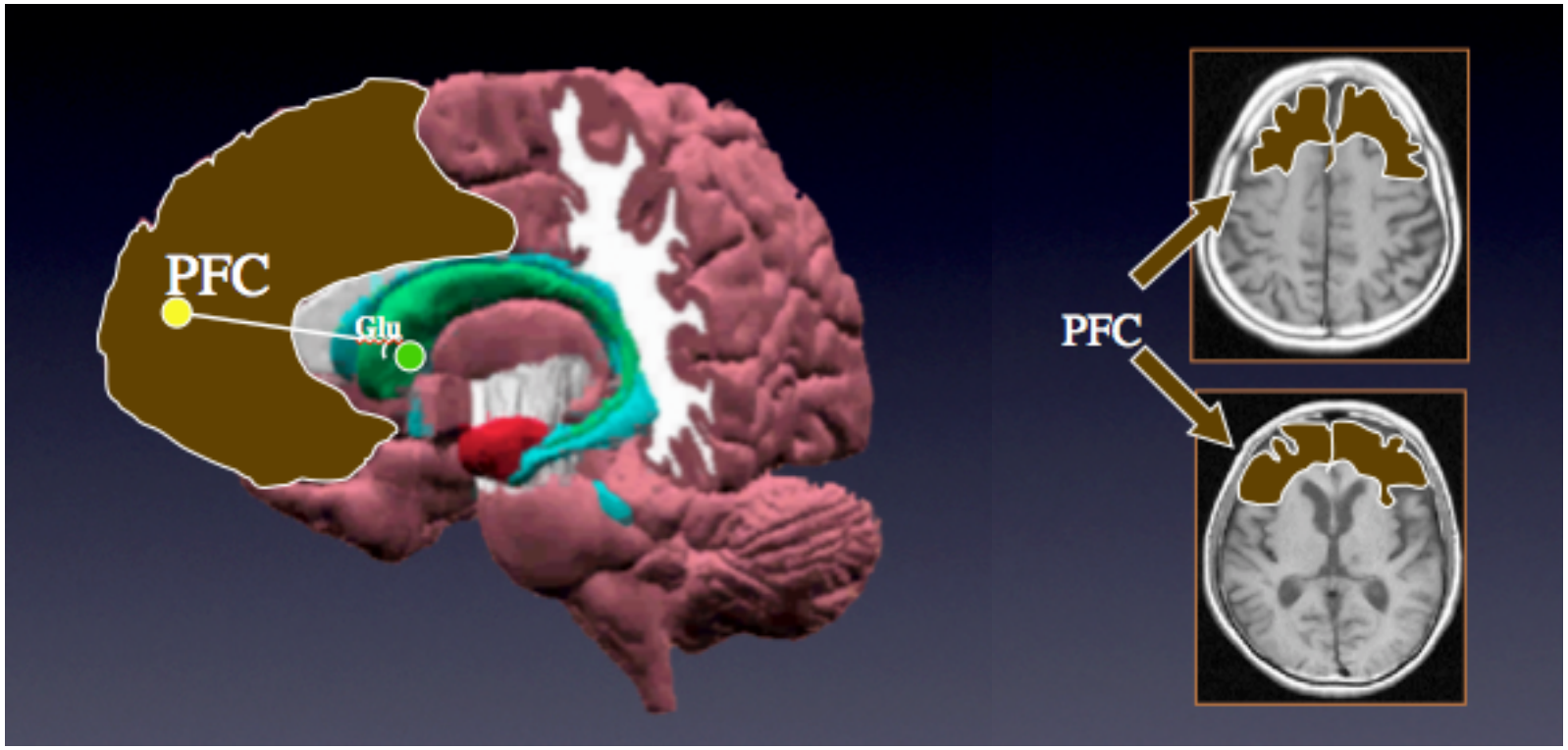
Neurobiology of Psychiatric Illnesses

Background:

1. Neurocircuitry
    - Frontal-subcortical circuits
    - Frontal-limbic circuits
2. Prefrontal cortical and limbic structures
3. Neurotransmitters
    - GABA
    - Glutamate
    - Mono-amines
        - Serotonin (5-HT)
        - Norepinephrine (NE)
        - Dopamine (DA)

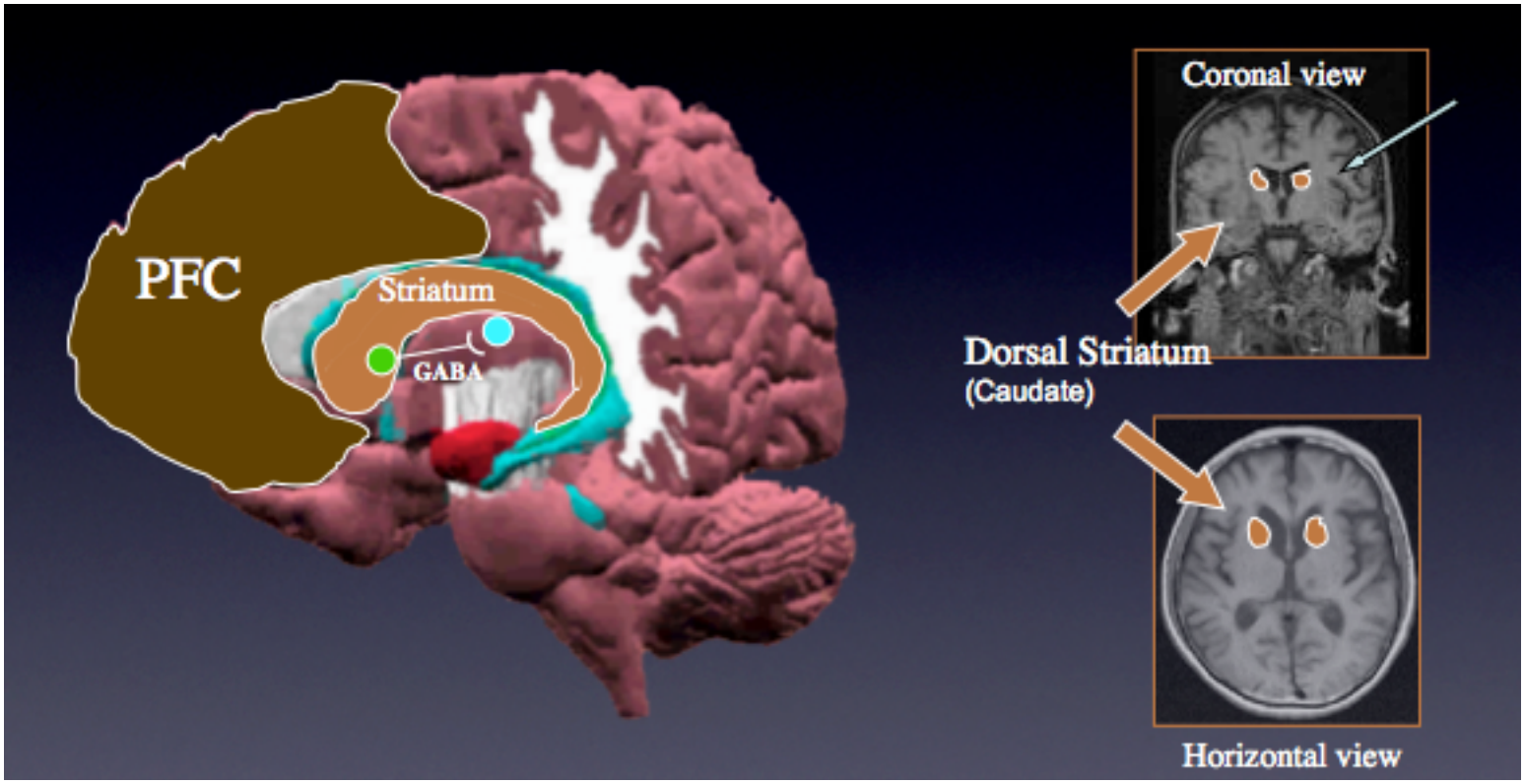


Cortical-Striatal-Thalamic Circuitry



Prefrontal cortex:
Glutamatergic neurons project to the striatum

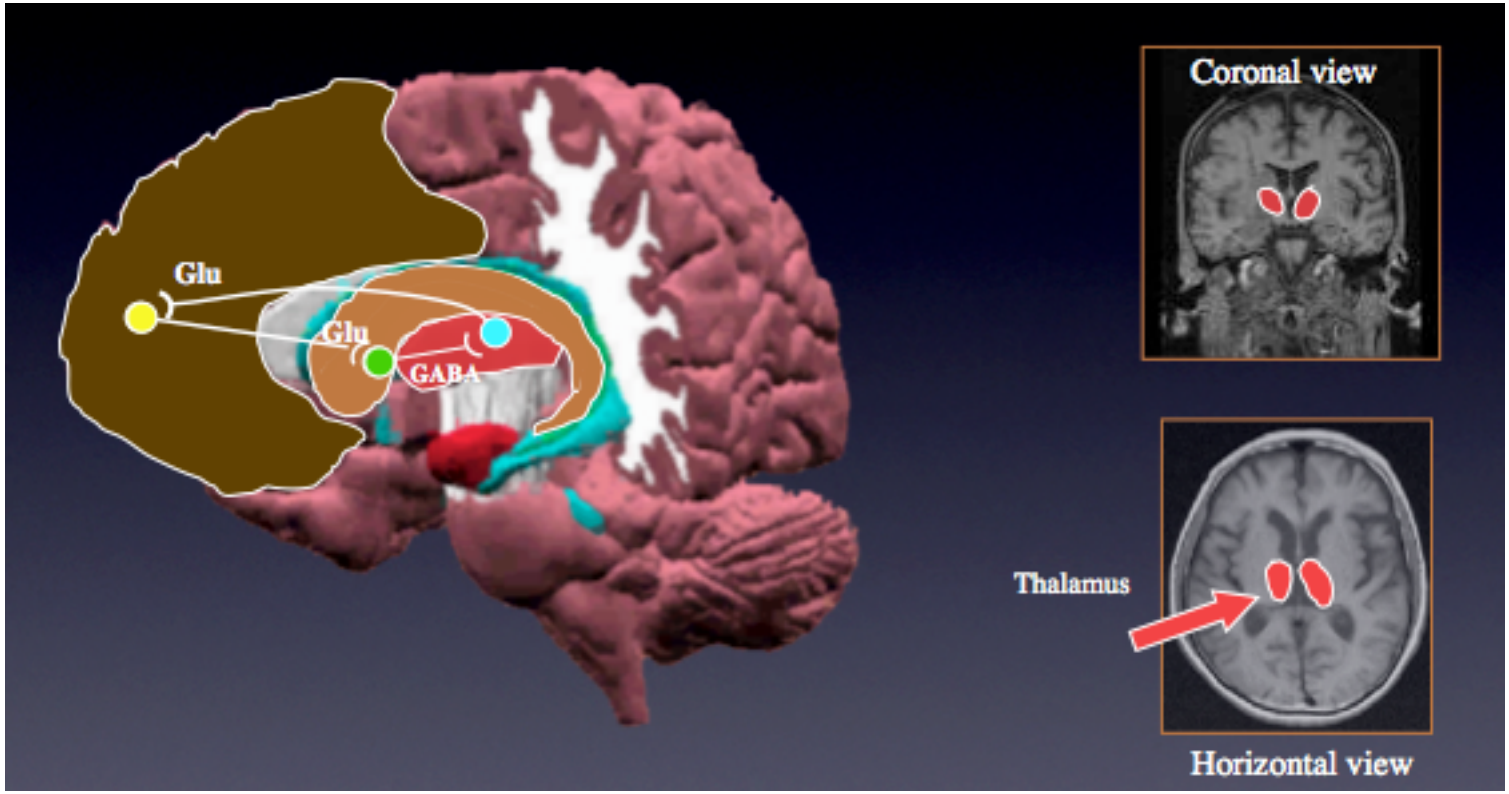
Cortical-Striatal-Thalamic Circuitry



The striatum is made up of GABAergic neurons and consists of distinct structures:

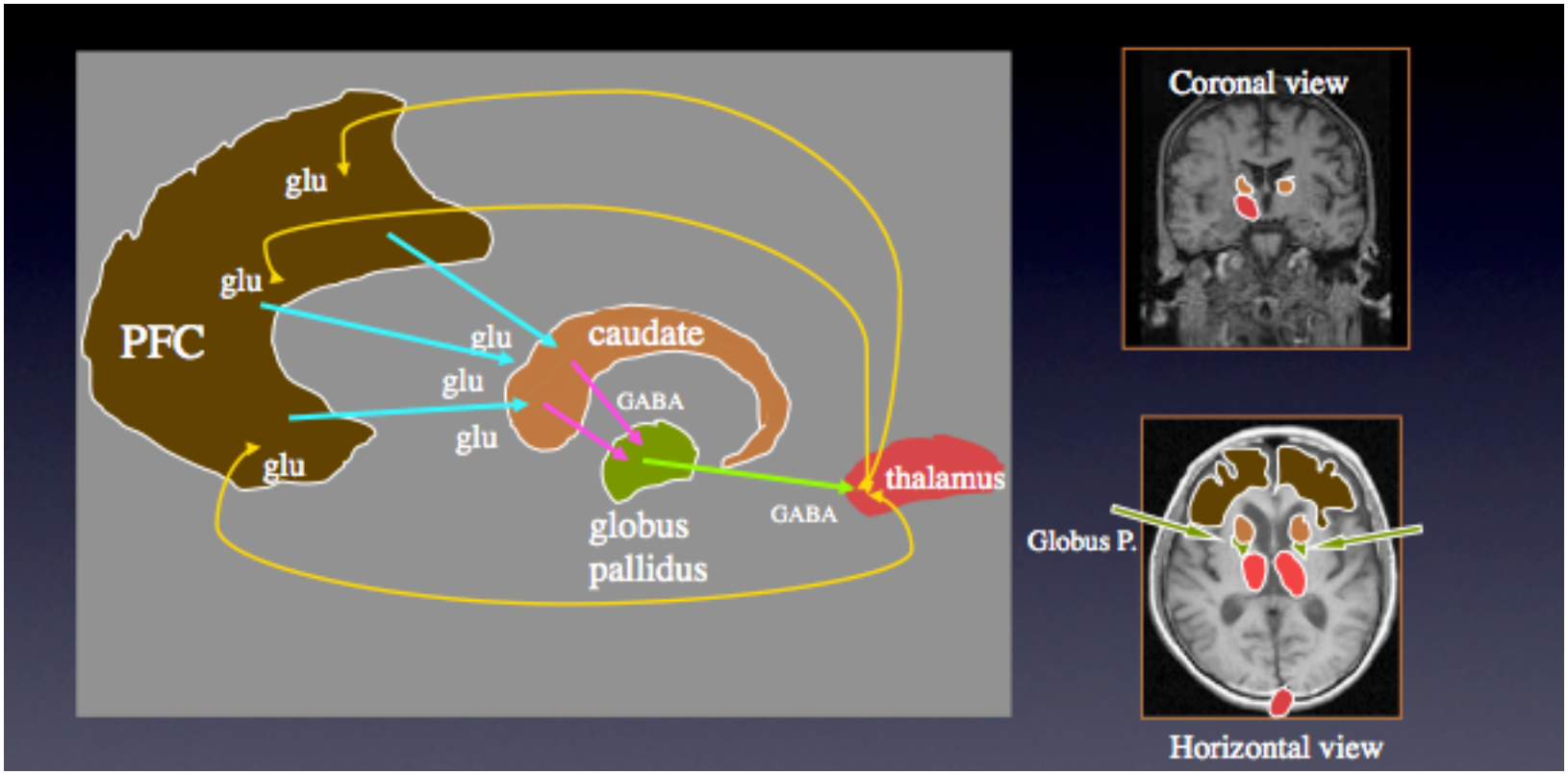
- Dorsal striatum (caudate, putamen)
- Ventral striatum (nucleus accumbens)

Cortical-Striatal-Thalamic Circuitry



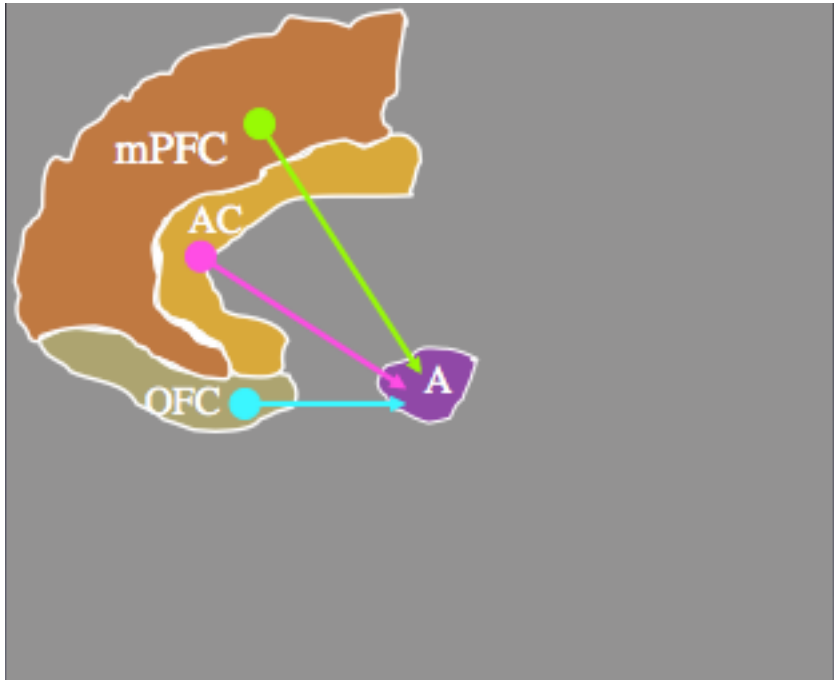
The thalamus is the final site of processing pre-frontal output information. This output then returns to the pre-frontal cortex through a glutamatergic pathway.

Cortical-Striatal-Pallidal-Thalamic Circuitry



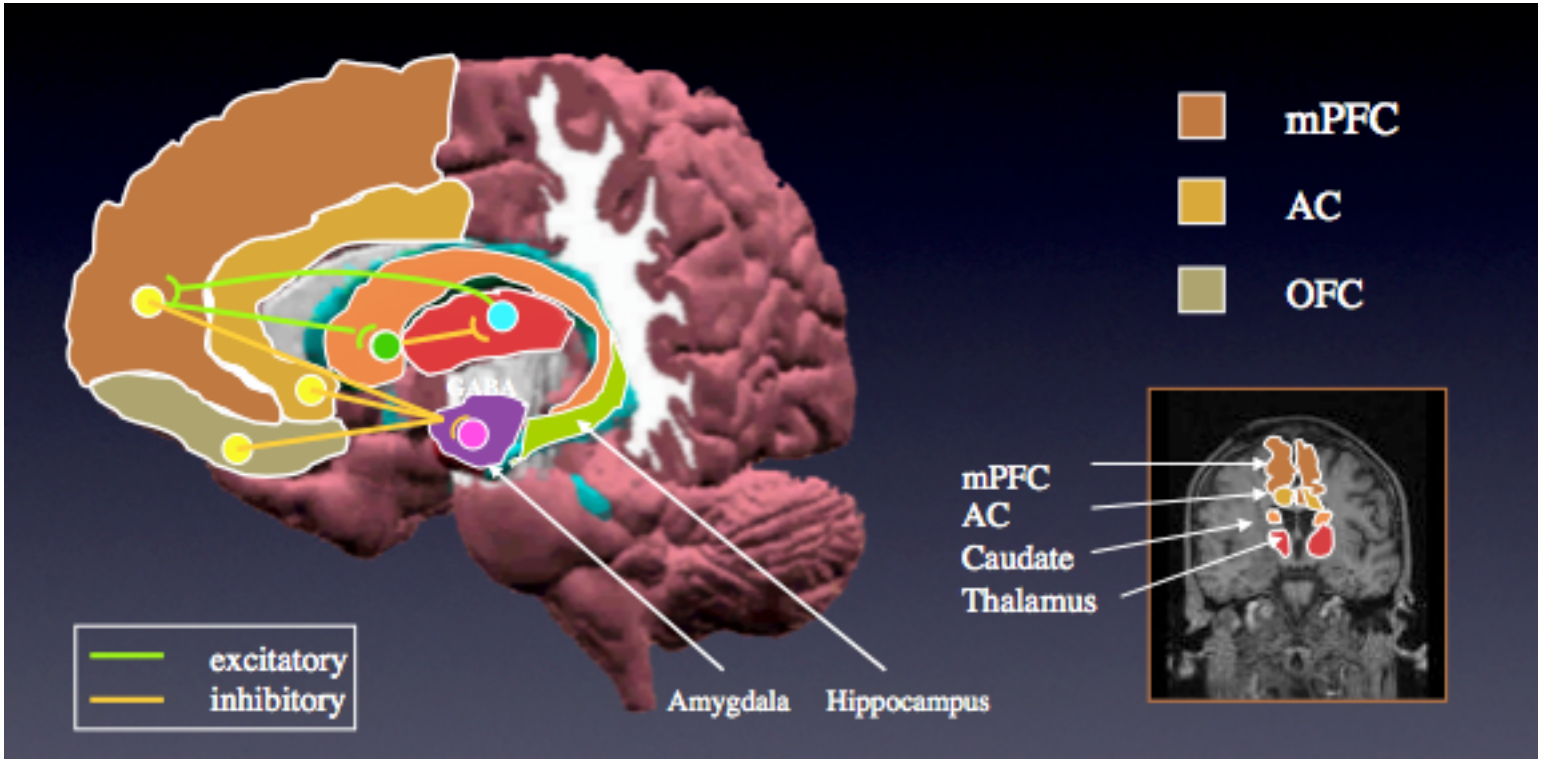
This is an expanded view of the circuit with glutamate and GABAergic projections, the global pallidus is here seen in green. Pallidal projections are GABAergic and go to the thalamus.

Cortical and Limbic Connections



- The pre-frontal cortex inhibits the amygdala
- The mPFC, OFC, and AC all inhibit amygdala activity
- When these structures are dysregulated, amygdala activity is less modulated by the PFC and emotional responses are less controlled. Fear may be easily aroused.

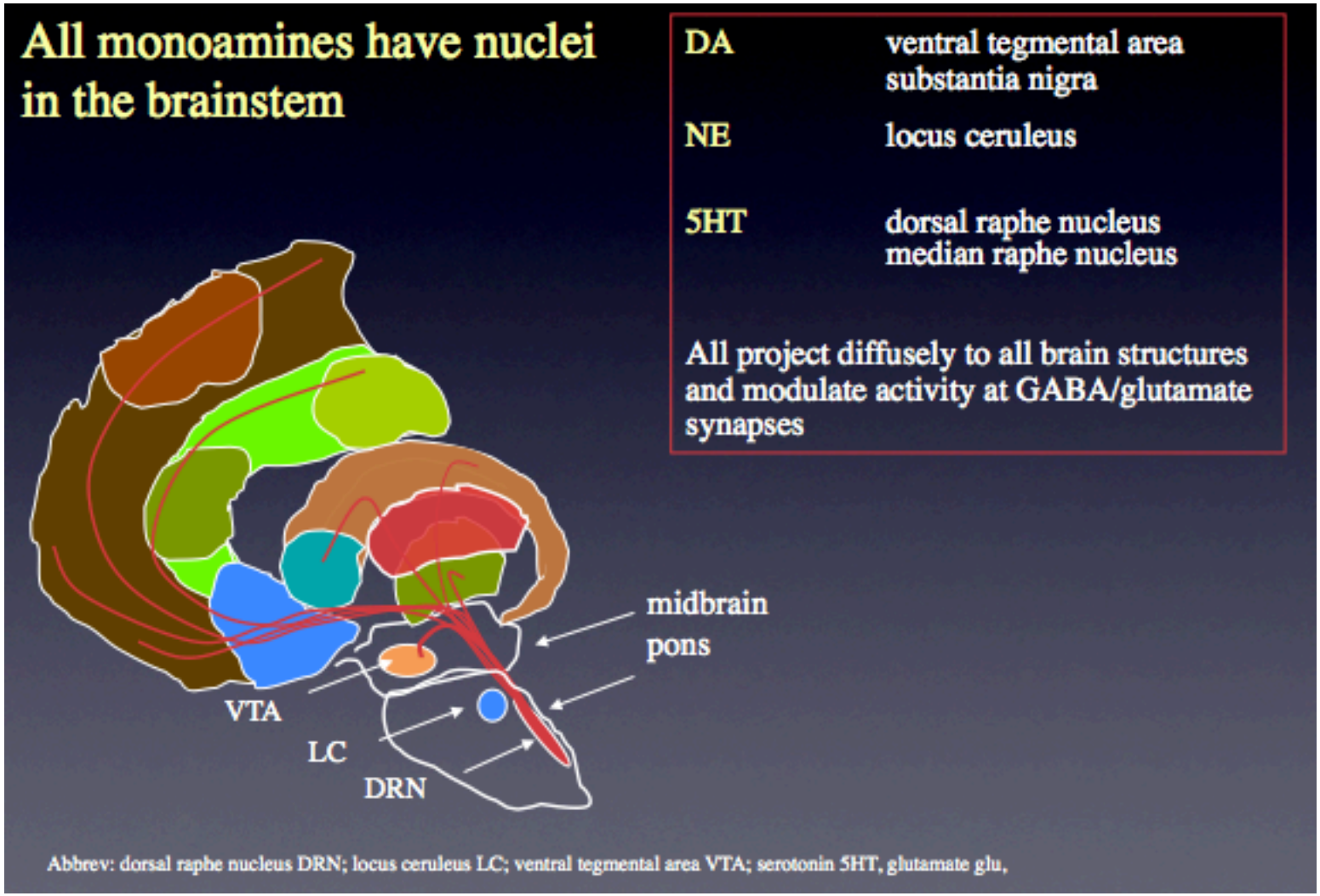
Cortical and Limbic Connections



When prefrontal-striatal-thalamic processing is dysregulated, prefrontal function inhibition of hippocampus and amygdala will be disconnected. This results in:

- Abnormal function of the mPFC, AC, and the OFC
- Anxiety, autonomic arousal, hypothalamic pituitary axis (HPA) activation

Cortical Limbic Connections: Role of Monoamines



Serotonin, Norepinephrine, and Dopamine

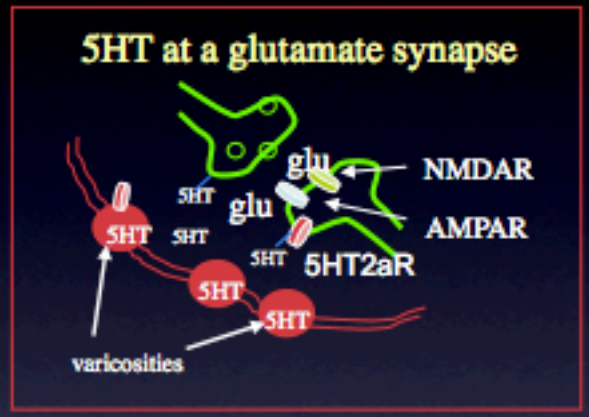
Cortical Limbic Connections: Role of Monoamines

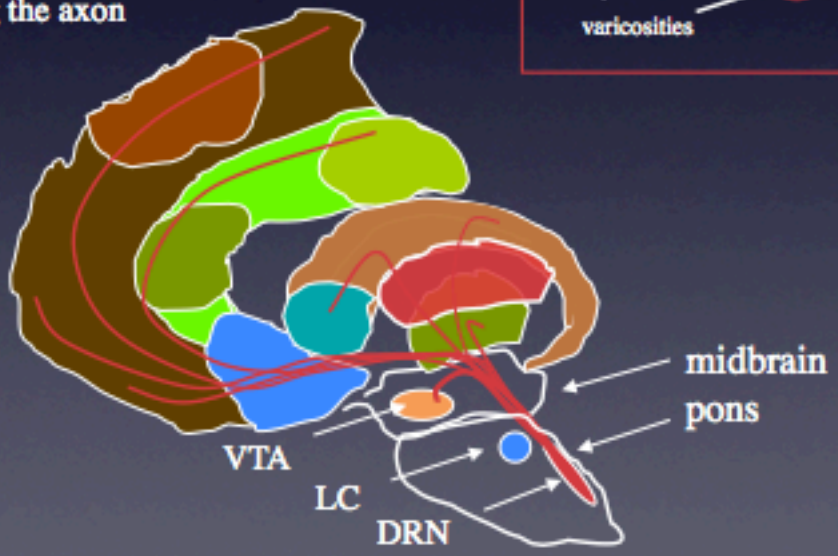
Example (see below and adjacent)

DA, NE and 5HT projections arise from brainstem nuclei

5HT modulates activity at glutamate and GABA synapses

5HT fibers bypass these synapses and release 5HT from varicosities along the axon





Summary of Functional Neuroanatomy Review

1. Neurocircuitry is important in understanding the neurobiology of psychiatric illness
    - Frontal-subcortical circuits
    - Frontal-limbic circuits
2. Prefrontal cortical structures regulate limbic areas
    - Amygdala
    - Hippocampus
3. Neurotransmitters found in these circuits
    - GABA
    - Glutamate
    - Mono-amines
        - ❖ Serotonin (5-HT)
        - ❖ Norepinephrine (NE)
        - ❖ Dopamine (DA)

Neurobiology of Psychiatric Illness:
Schizophrenia

Neurobiological Abnormalities in Schizophrenia

- Dopamine and glutamatergic hypothesis
- Brain volume changes:
    - ❖ prefrontal cortex
    - ❖ limbic structures
- Working memory deficits: inefficient cortical processing
- Genetic polymorphisms in schizophrenia
    - ❖ COMT val-met polymorphism and effect on working memory
- Postmortem molecular, cellular and structural abnormalities
- Neurodevelopmental animal model of schizophrenia
- Neurodevelopmental vs. Neurodegenerative models of schizophrenia

Schizophrenia

Definition: mental disorder characterized by abnormal social behavior and failure to understand what is real.

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

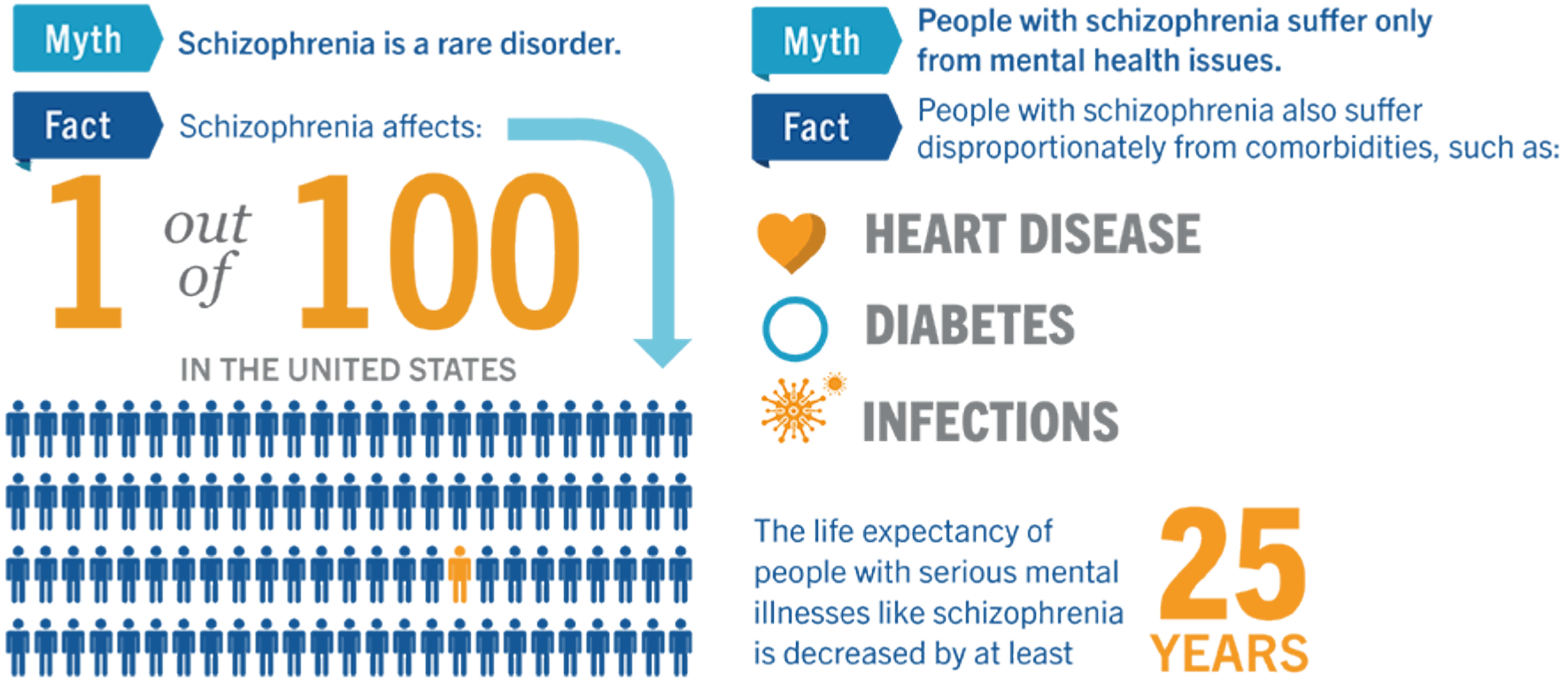
Cognitive –

- 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

Schizophrenia

John Forbes Nash

Common Misconceptions



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 – note that this does result in fewer treatment options for negative symptoms.

Dopaminergic Hypothesis

The dopamine hypothesis of psychosis attributes symptoms of schizophrenia to a disturbed and hyperactive dopaminergic signal transduction:

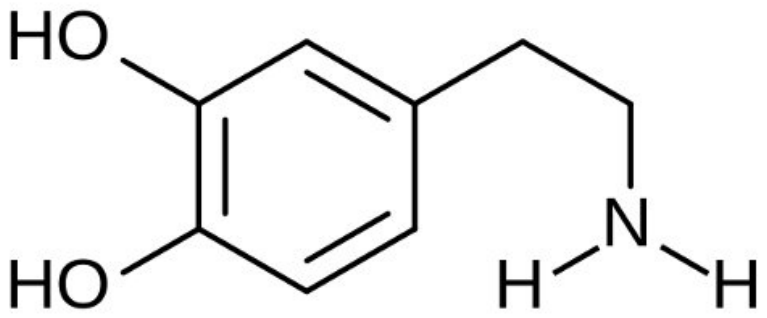
Mesolimbic Structures: Hyper-dopaminergic

Ventral striatum (nucleus accumbens, olfactory tubercle),
Bed nucleus of stria terminalis, amygdala, lateral septal nucleus, dorsal striatum

Mesolimbic Structures: Hypo-dopaminergic

Entorhinal cortex and Pre-frontal cortex

Results in overactive limbic areas
Poor pre-frontal/executive function



Dopamine

Hypo-glutamatergic Hypothesis

Consequence of hypo-functional glutamatergic neurons in the pre-frontal cortex

- Abnormal cortical feedback to ventral tegmental area (VTA)
- Disinhibits the VTA causing increased dopamine release in limbic areas
- Disinhibits substantia nigra, causing increased dopamine release in dorsal striatum

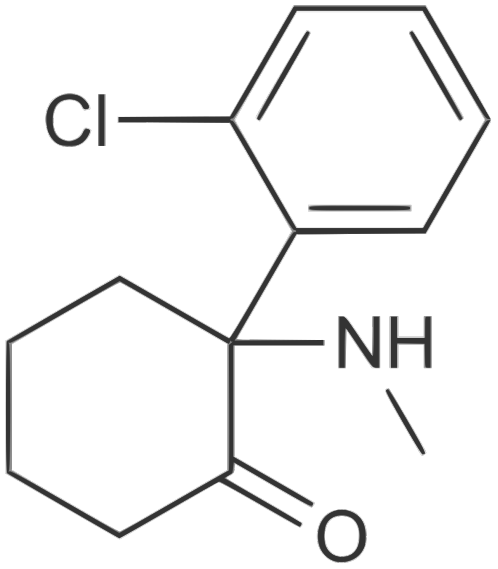
Results in abnormal regulation of both cortical glutamate and GABA

Hypo-glutamatergic hypothesis

During neurodevelopment, this hypo-glutamatergic state results in abnormal connectivity and function of PFC and limbic areas. This causes inefficient cortical processing and both positive and negative symptoms.

Pharmacologic model of schizophrenia

Negative and positive symptoms are mimicked by the NMDA glutamate receptor antagonist ketamine



Test Your Understanding:

1. Which of the following is **not** a positive symptom of schizophrenia?
    A. Delusions
    B. Disorganized thinking and speech
    C. Alogia (an inability to speak)
    D. Hallucinations

2. The dopaminergic hypothesis of schizophrenia suggests that there is excess dopamine activity in the _____, but unusually low dopamine activity in the _____.
    A. Limbic system; Prefrontal area
    B. Mesolimbic system; Prefrontal area
    C. Prefrontal area; Limbic system
    D. Thalamus area; Mesolimbic system

Test Your Understanding:

1. Which of the following is **not** a positive symptom of schizophrenia?
    A. Delusions
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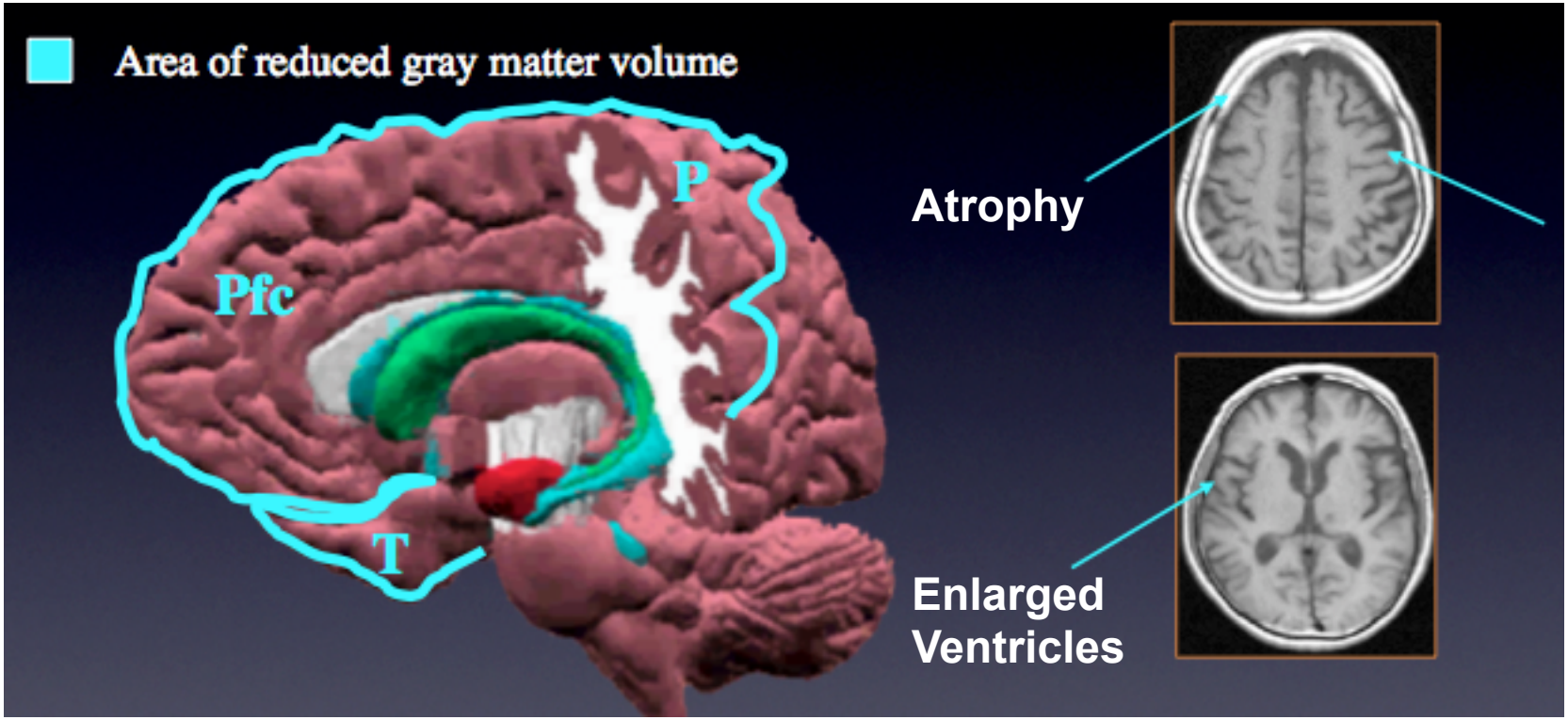
    B. Mesolimbic system; Prefrontal area
    C. Prefrontal area; Limbic system
    D. Thalamus area; Mesolimbic system

Multiple brain structures are reduced in volume in schizophrenia

Prefrontal cortex
Temporal cortex
Ento-rhinal cortex
Para-hippocampal cortex
Hippocampus

Decreased total gray matter volume:
Overall (7%), regionally-frontal (PFC), parietal, and temporal shown below



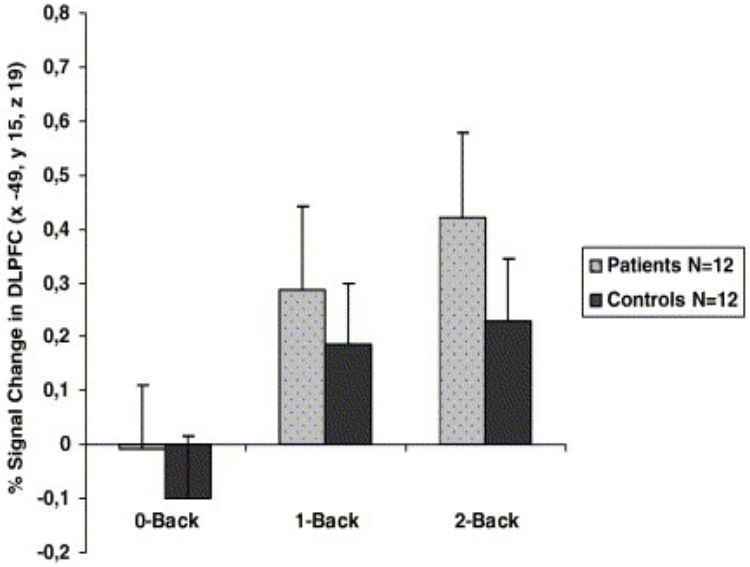
Genetic Polymorphisms in Schizophrenia

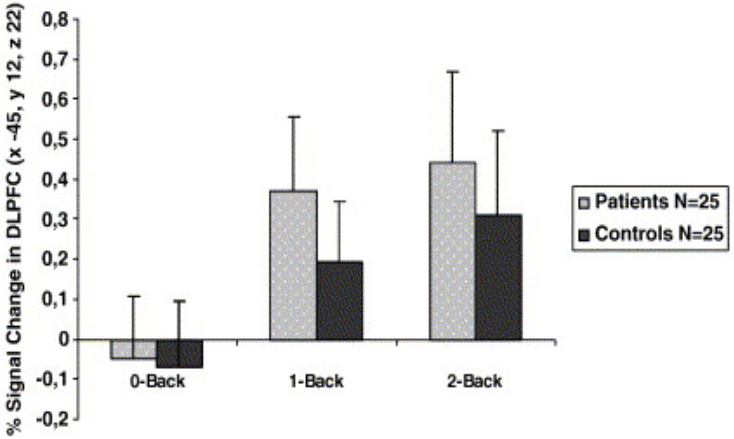
Polymorphism: the presence of genetic variation within a population, upon which natural selection can operate

In schizophrenia subjects, polymorphism of the catecho-O-methyl transferase (COMT) is associated with PFC dysfunction

- Results in impaired working memory
- COMT metabolizes dopamine and norepinephrine at the synapse
- COMT polymorphism at position 158: val to met
  - ❖ Val-val genotype has increased enzymatic activity, hence lower dopamine (DA) levels at synapse (DA more rapidly cleared than val-val or met-met)
  - ❖ Met-met genotype has less enzymatic activity, and dopamine levels at the synapse are higher (DA more slowly cleared from synapse)
- DA levels act to 'fine tune' glutamate release and PFC processing to maximize performance during working memory tasks

Genetic Polymorphisms in Schizophrenia

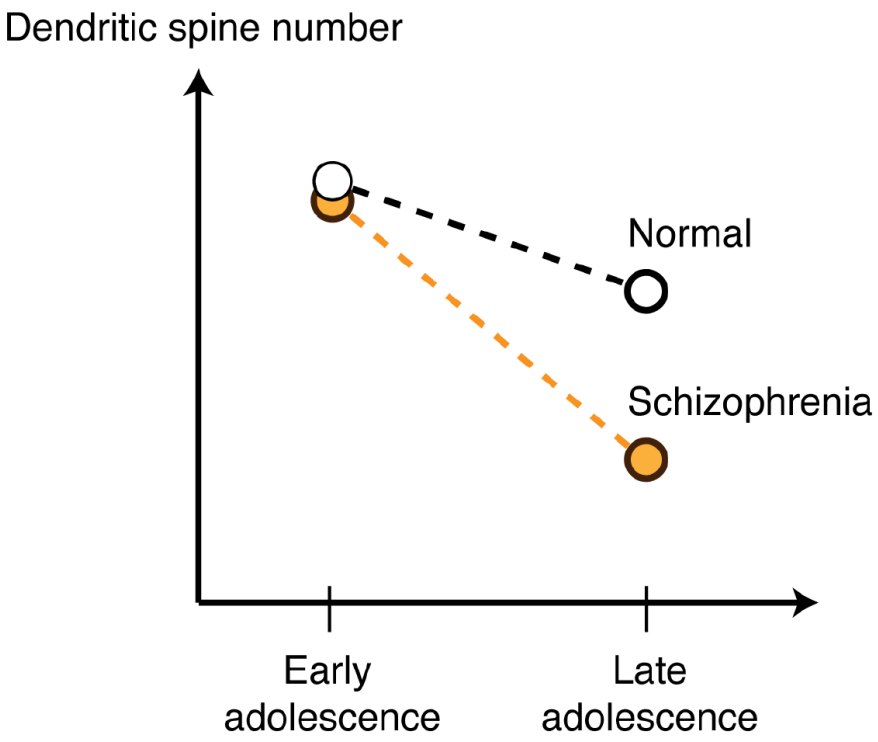




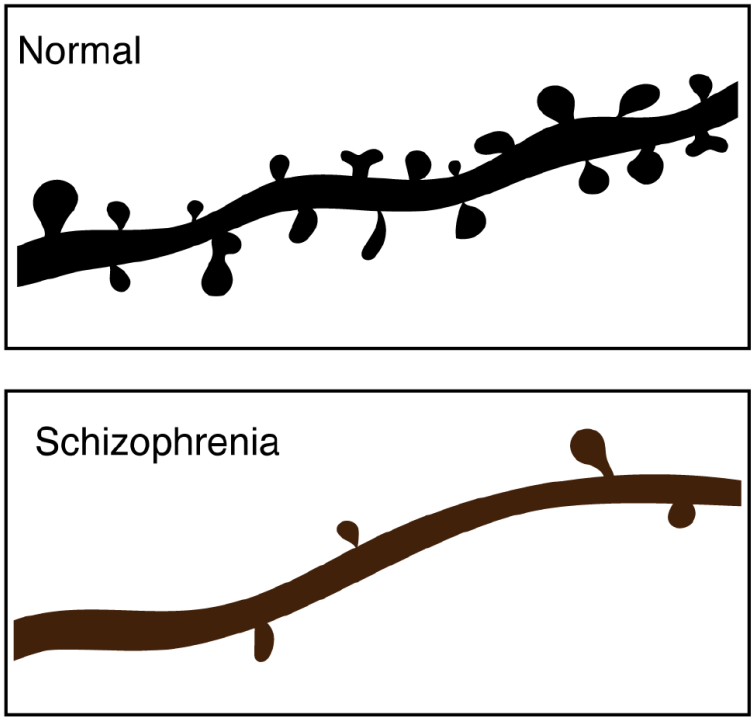
- 'N-back' test examines working memory, which depends on activation of dorso-lateral PFC (DLPFC)
- Schizophrenic subjects had a greater increase in metabolic activity in the DLPFC as the difficulty increased (brain has to work harder to do the same task as controls)
- This indicates that schizophrenic subjects have inefficient pre-frontal activation in an executive function task (working memory)

Loss of Spines in Schizophrenia

(A)



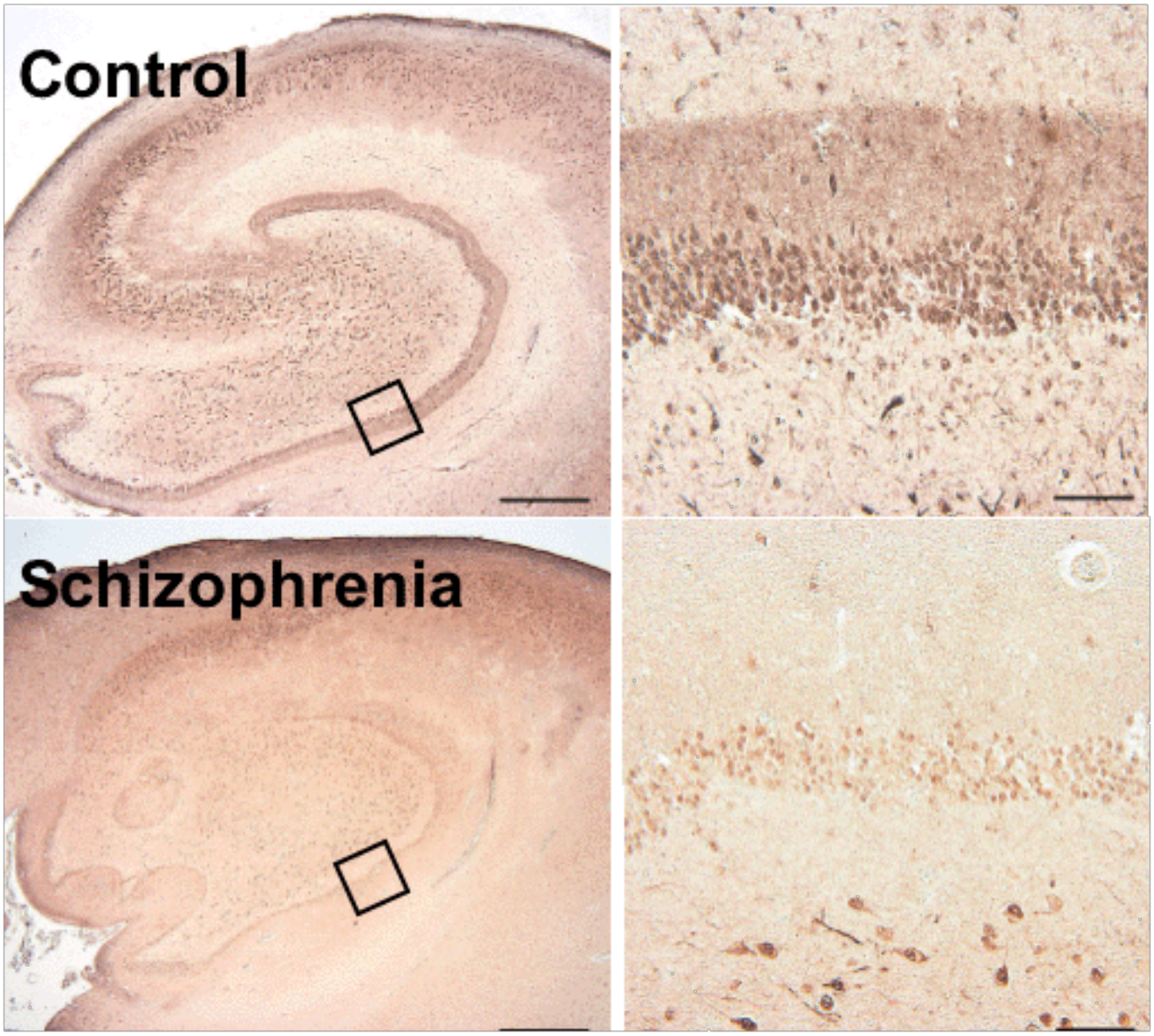
(B)



(A) While a decrease in synapse number during late adolescence and early adulthood is a part of normal development, schizophrenia patients show a greater loss in synapses.

(B) Post-mortem studies show an abnormal decrease in dendritic spine density in neurons.

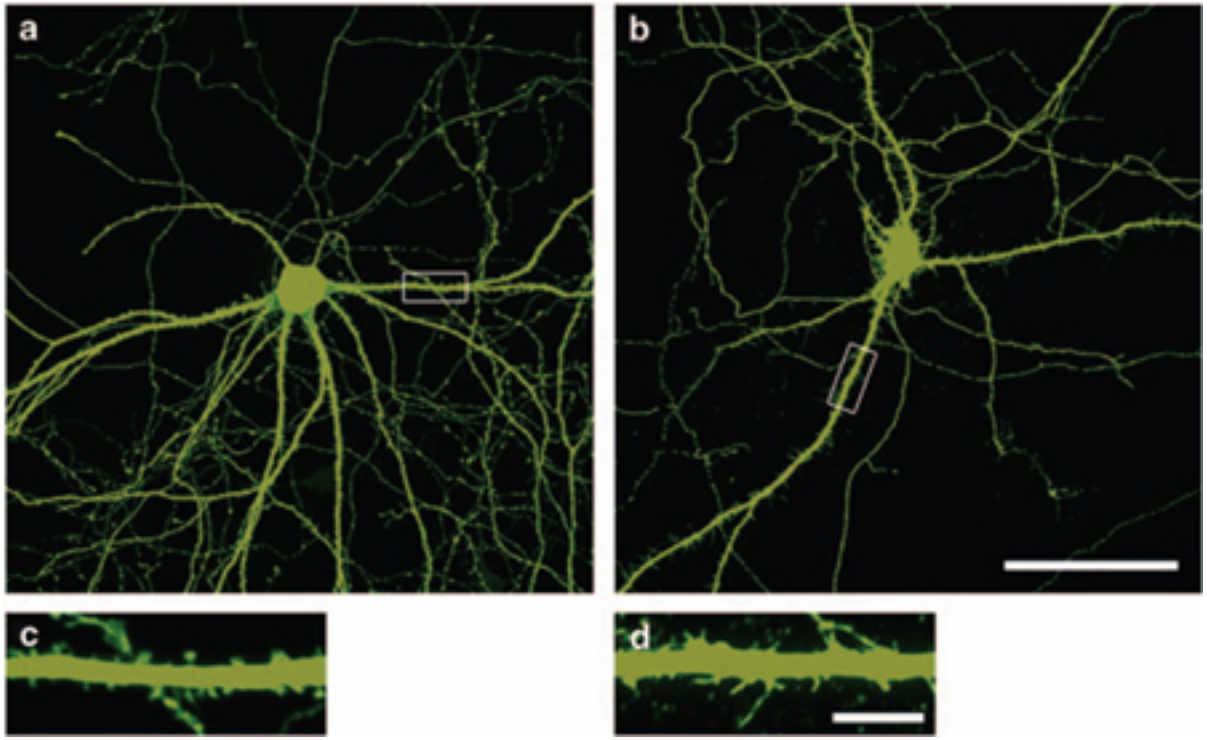
Post-mortem studies



The abnormality most prominent was in the dentate gyrus portion of the hippocampus, which is important for short-term memory. There is also a loss in dysbindin protein.

(Arnold et al, 2004)

The Schizophrenia Susceptibility Gene *Dysbindin* Regulates Dendritic Spine Dynamics



a. Primary cultured rat hippocampal neurons transfected with GFP plus dysbindin vector
b. Neuron after 4 days, stained with anti-GFP
c. Magnified image of **a.**
d. Magnified image of **b.**

Post-mortem studies

- Increased cell number, reduced gray matter, increased neuropil: pre-frontal and auditory cortex, caudate, lateral nucleus of amygdala
- Abnormal migration of cortical pyramidal cells in development found deep in white matter; remnant of migrating cells in developing brain
- Abnormalities in oligodendrocytes
- Abnormalities affecting neuronal maturation, survival, plasticity, synaptic integrity (synaptophysin, growth associated protein-GAP43)
- Abnormalities in glutamate synapes in DLPFC: decreased binding of kainate receptors
- Abnormalities in GABA, Glu, DA neurotransmitter systems or synapses, in DLPFC and elsewhere: neuropeptide Y and CCK

Sources:
Selemon LD,.Biol Psychiatry 45:17-25 (1999. .Kreczmanski P,et al. Brain 130:678-692 (2007) Knable M et al. Mol Psychiatry 7(4):392-404 2002
Hashimoto Tet al. Molec Psychiatry epub 1 May (2007). Flynn S et al. Mol Psychiatry 8(9):811-820 (2003). Weickert C et al. Cereb Cortex 11(2): 136-47 (2001).
Scarr E et al. Neuropsychopharmacology 30(8):1521-1531.

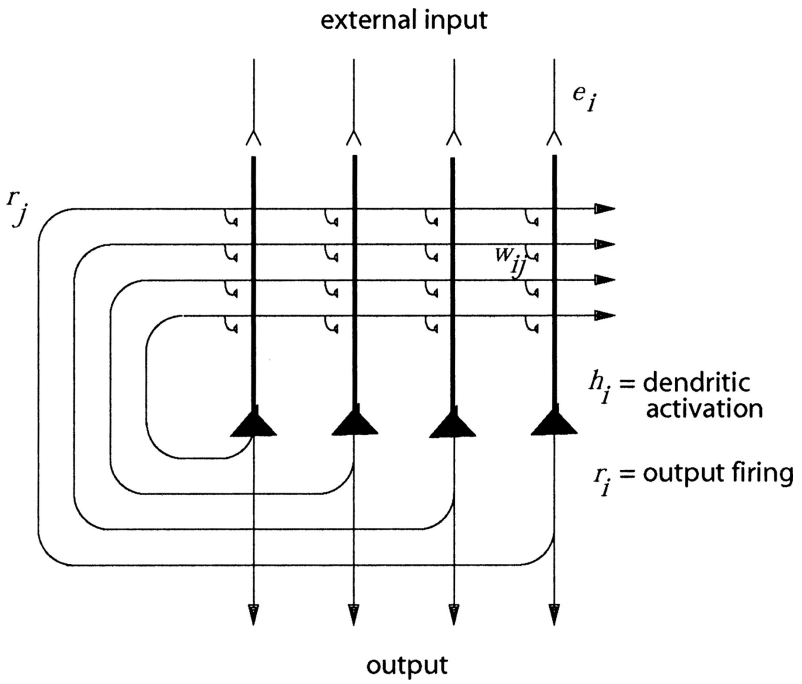
Neurodevelopmental vs. Neurodegenerative Processes in Schizophrenia

- Higher risk due to prenatal, perinatal, postnatal exposure to neuronal insult such as infection, hypoxia, hypoglycemia, hypercortisolism, or genetic vulnerability
- Abnormalities noted early in life: cognitive, motor, and social
- Enlarged ventricles (cavities in brain where cerebrospinal fluid is produced)
- Reduced pre-frontal gray matter volume over time, as well as reduced N-acetyl aspartate (NAA is a marker of neuronal number), may be a neurodegenerative process due to excito-toxic glutamatergic activity
- Schizophrenia may be due
    - ❖ Neurodevelopmental abnormalities
    - ❖ Neurodegenerative abnormalities
    - ❖ Both, in at least some individuals

Lewis D et al. Annu Rev Neruosci 25:499-532 (2002).

Computational Models of Schizophrenia

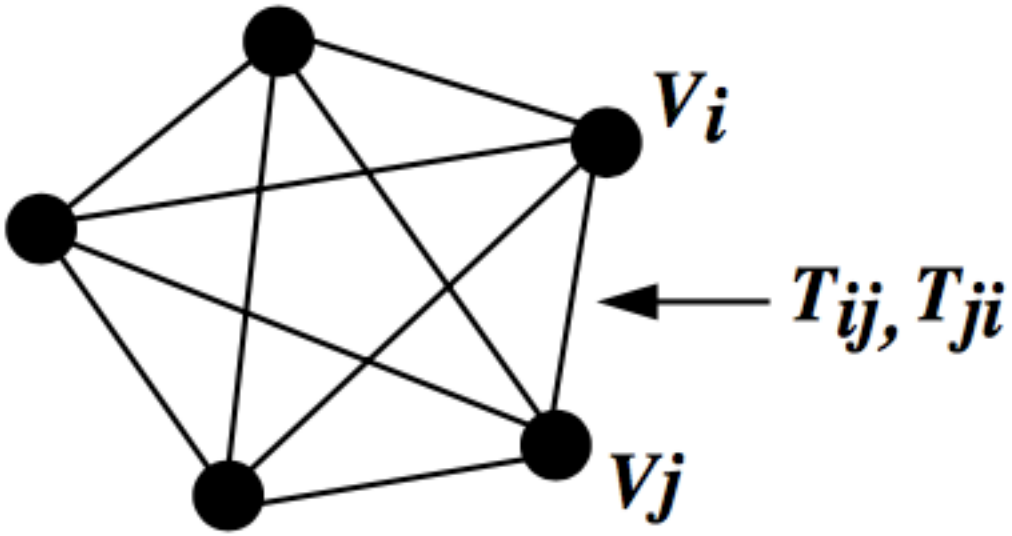
Challenge: the disease is complex and heterogeneous
Models involving **neural networks** have begun to address how this disorder has divergent symptoms.



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

Modeling Schizophrenia: Attractor Networks



V_i: *denotes activity state of* ***neuron i*** *in the network*

T_{ij}: *denotes strength of the connection from* ***neuron j*** *to* ***neuron i***

Attractor Neural Network: recurrent neural network with symmetric connections that act in two ways

$$V_i \rightarrow 1 \quad \text{if} \quad \sum_{j \neq i} T_{ij} V_j > 0$$

$$V_i \rightarrow -1 \quad \text{if} \quad \sum_{j \neq i} T_{ij} V_j < 0$$

Each neuron has two states, **+1 and -1**, and changes its state, V_i, according to rule on left

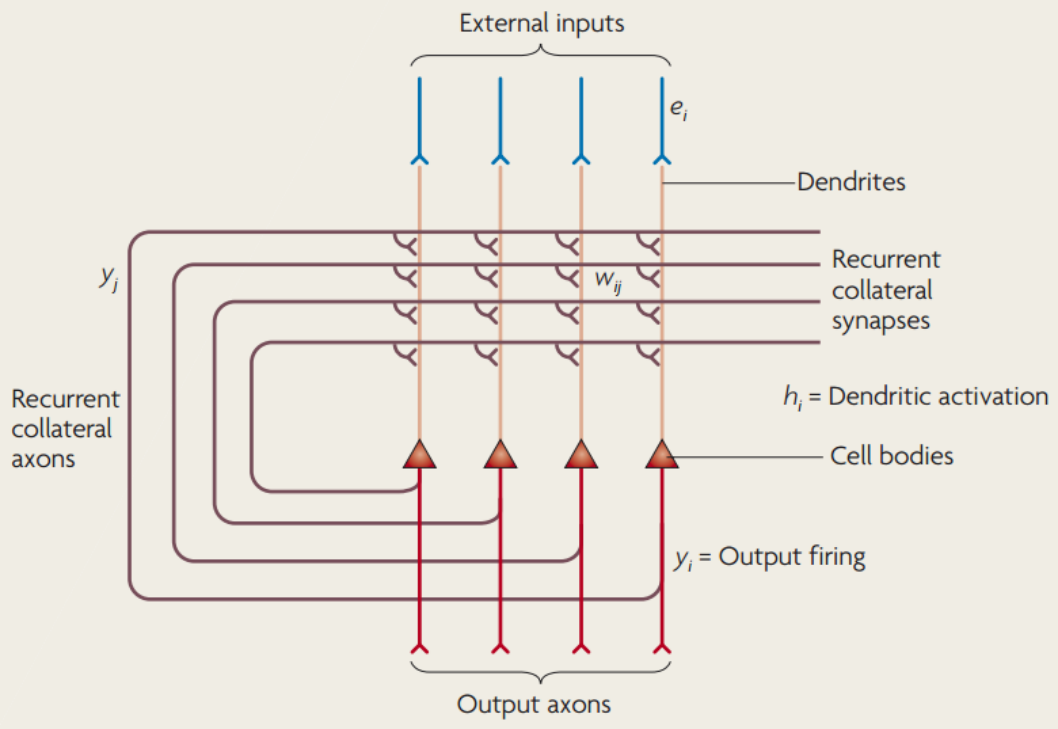
Attractor Networks

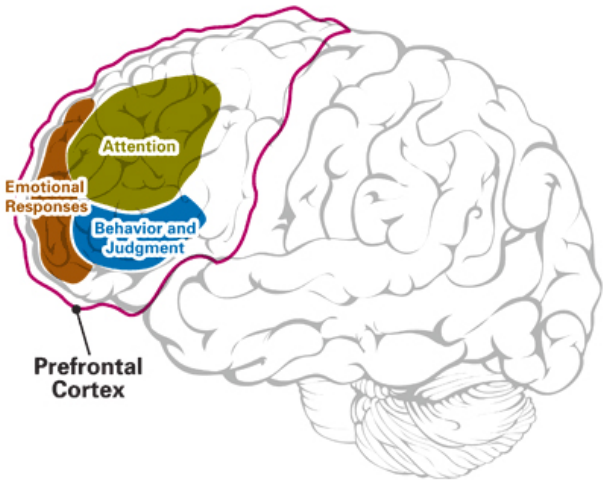
Used to model cognitive symptoms of schizophrenia.

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.

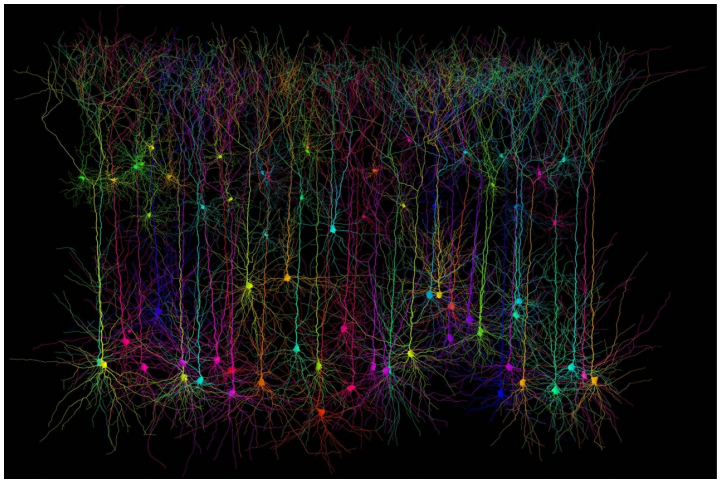
Attractor networks operate in the prefrontal cortex and can contribute to short-term memory and attention.



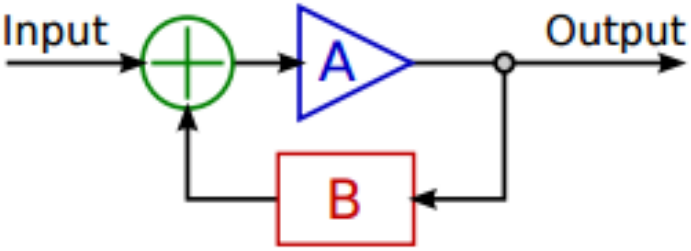


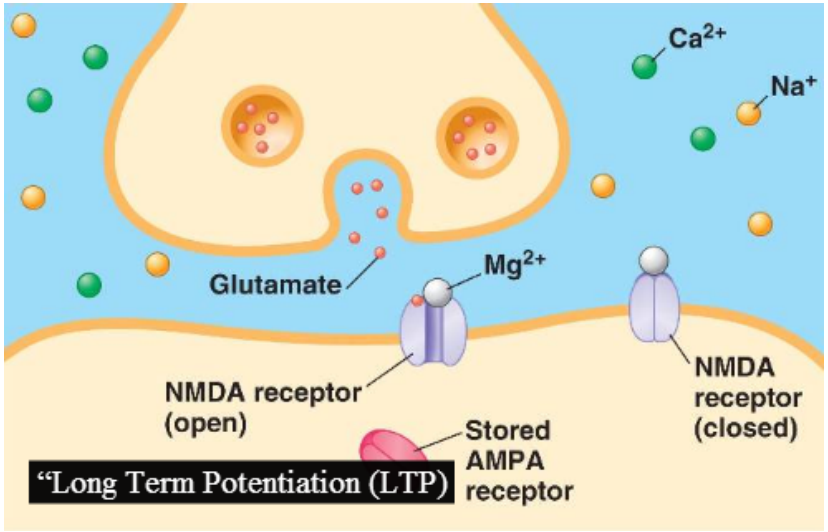
Biological Motivation

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.



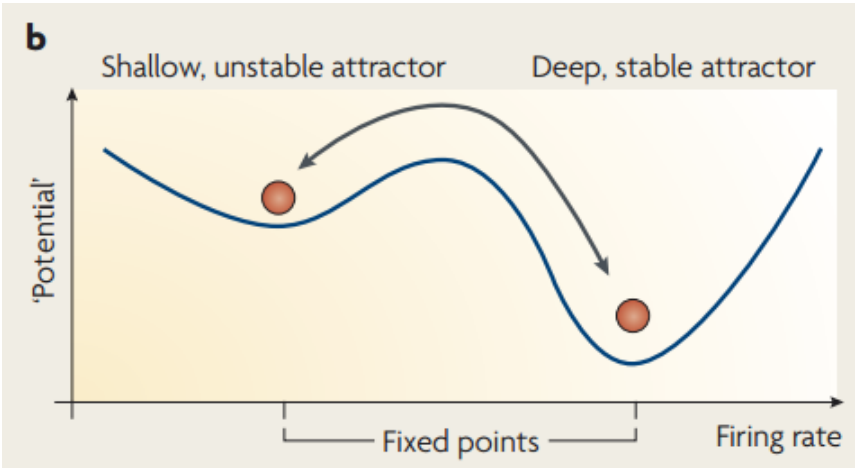


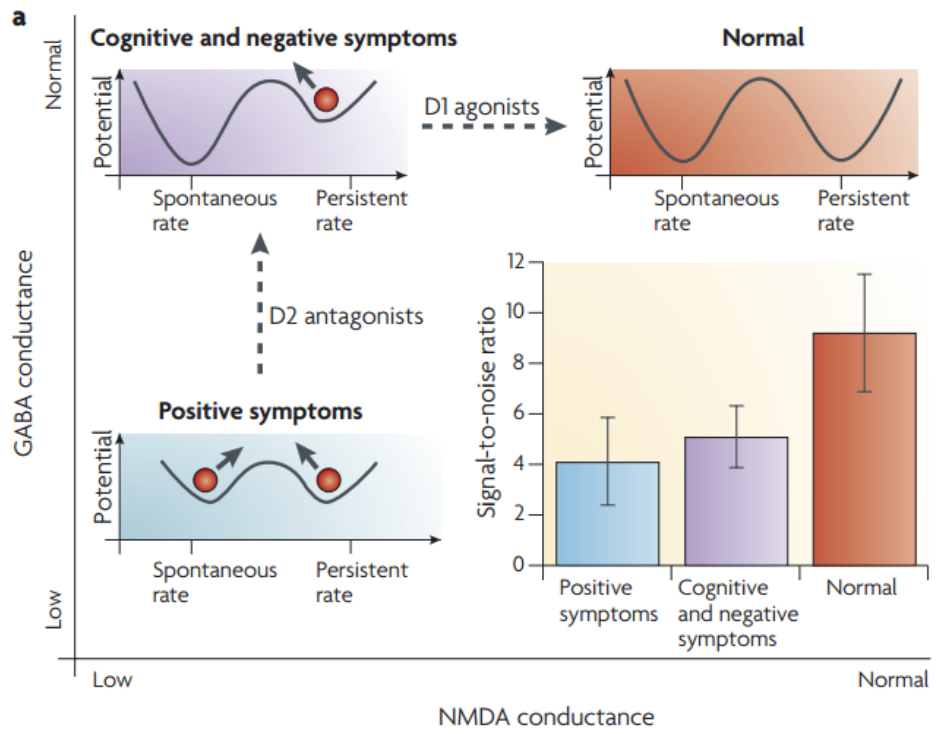
Forming a memory involves strengthening the excitatory connections between that set of neurons (**long-term potentiation**).

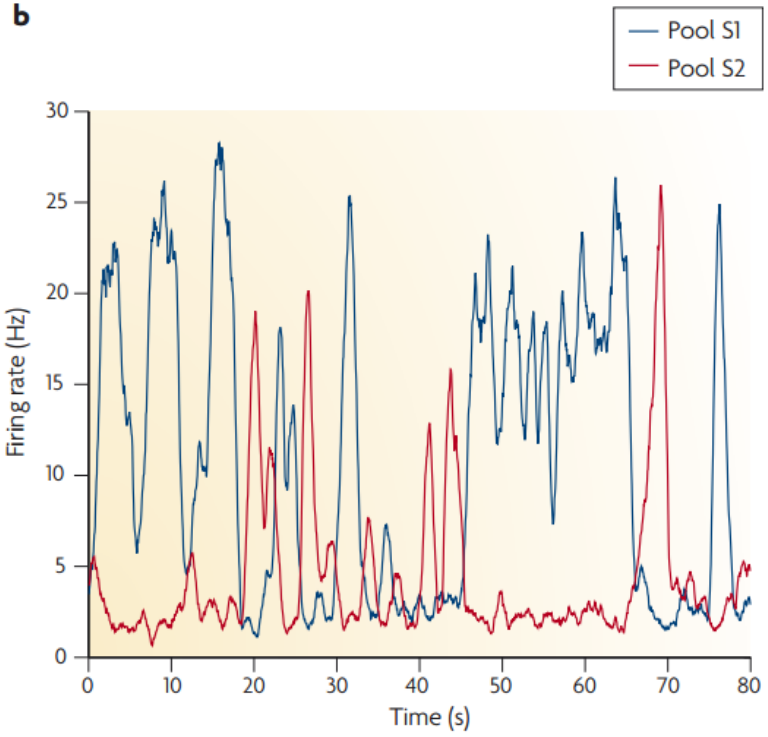
Stability of Attractor Networks

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

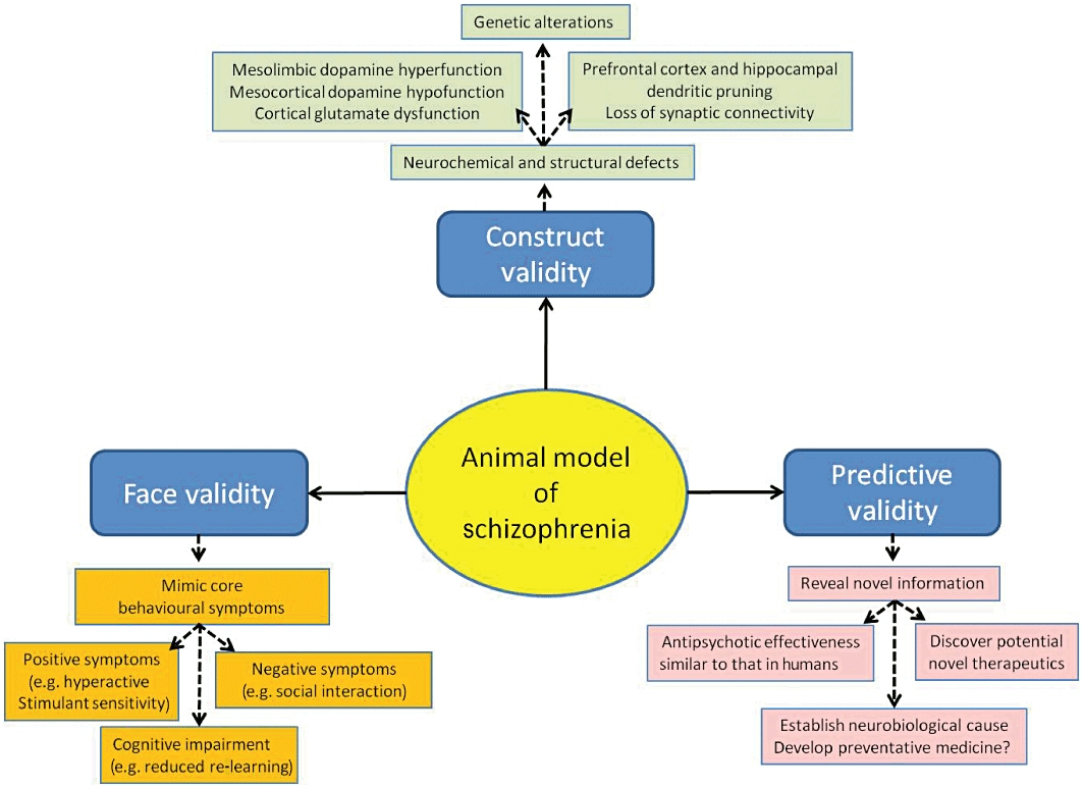
Different types of models:

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

- Dopamine
- Glutamate
- Serotonin
- GABA

Lesion

- Neonatal lesion



Test Your Understanding:

Circle whichever is greater, A or B. If A = B, circle both:

I.

A. permeability of a neuronal membrane to Na^+ during the rise phase of an action potential

B. permeability to K^+ at the same time

II.

A. speed of conduction of nerve impulse in neuron with diameter of 10 microns

B. speed of conduction of nerve impulse in neuron with diameter of 5 microns

III.

A. number of directions action potential will travel if stimulated at axon

B. number of directions action potential will travel if stimulated at dendrite

Test Your Understanding:

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A. permeability of a neuronal membrane to Na^+ during the rise phase of an action potential

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B. speed of conduction of nerve impulse in neuron with diameter of 5 microns

III.

A. number of directions action potential will travel if stimulated at axon

B. number of directions action potential will travel if stimulated at dendrite

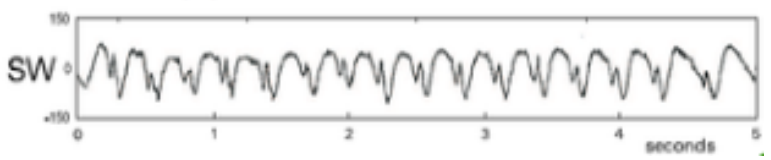
<u>Explanation:.</u> In A, action potential travels down axon. In B, local potentials will be produced and when the axon hillock is reached, it will stimulate action potential down axon.

Epilepsy

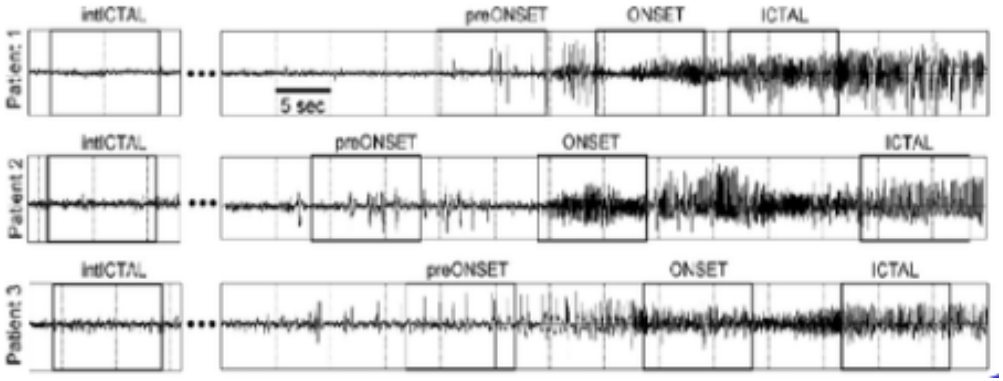
Epilepsy
Chronic Illness
Affects 1% to 2% of world population
40% of patients refractory to medication
Surgery available as treatment

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

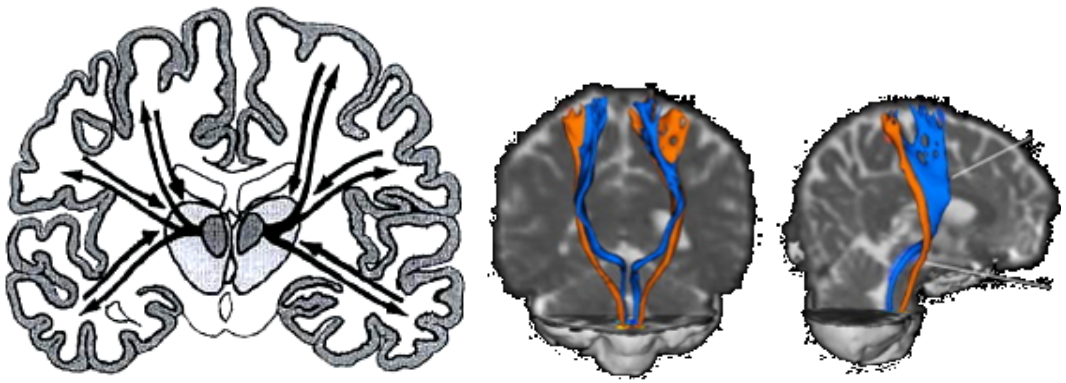
Generalized: Absence "petit mal"
Impairment of consciousness
Abrupt start and termination
Short duration
Unpredictable

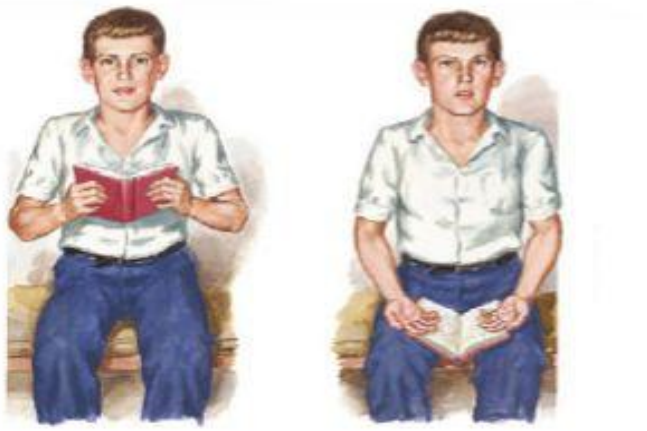


Generalized: Tonic-Clonic ("grand mal")
Rhythmic muscle contractions
Loss of consciousness



Childhood Absence Epilepsy

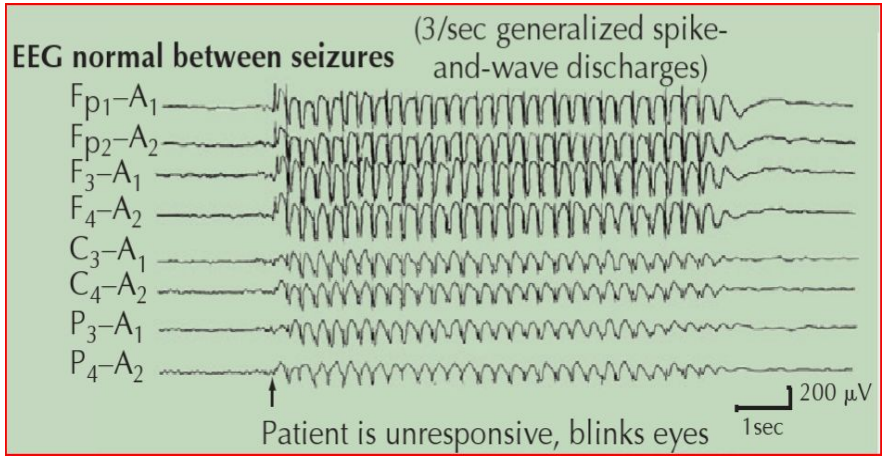




Pathophysiology of an Absence Seizure

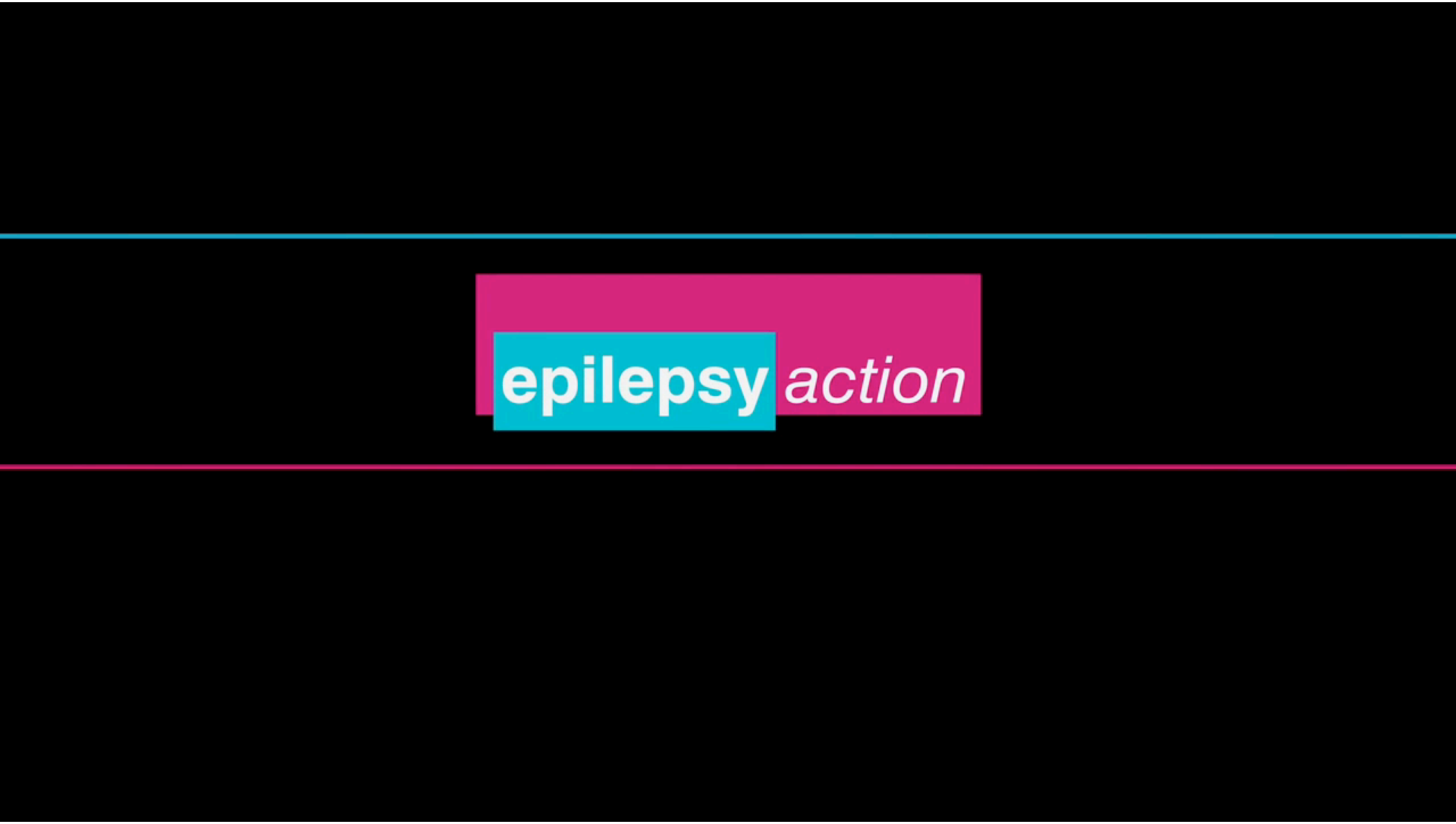
On Left: Corticoreticular Theory. Focal point or initiation site of absence seizure is in somatosensory cortex. Rhythmic oscillations between cortex and thalamus drive each other to propagate the spike-wave discharges of an absence seizure.

On Right: Oscillations are proposed to propagate along the corticoreticular pathway (blue).

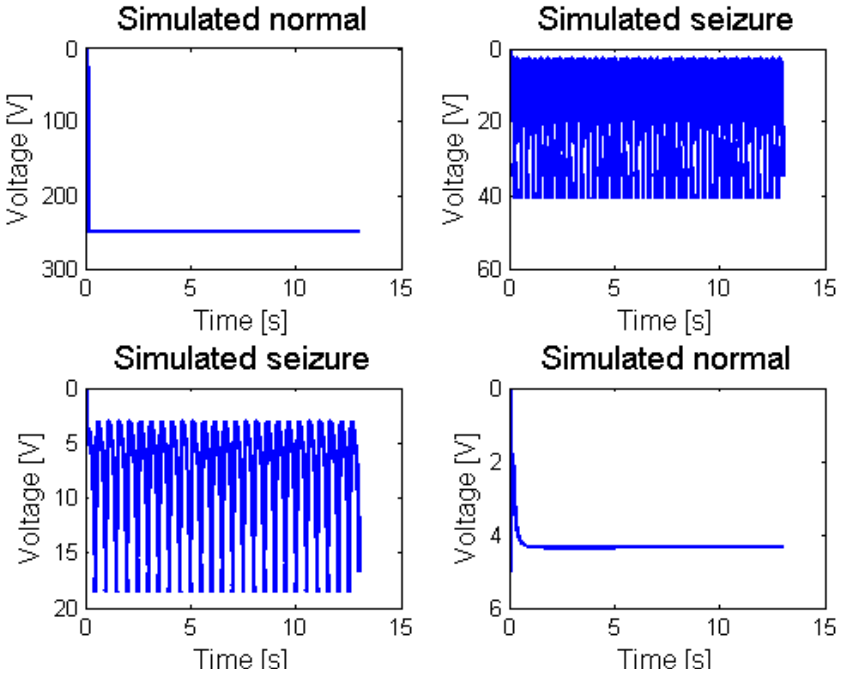


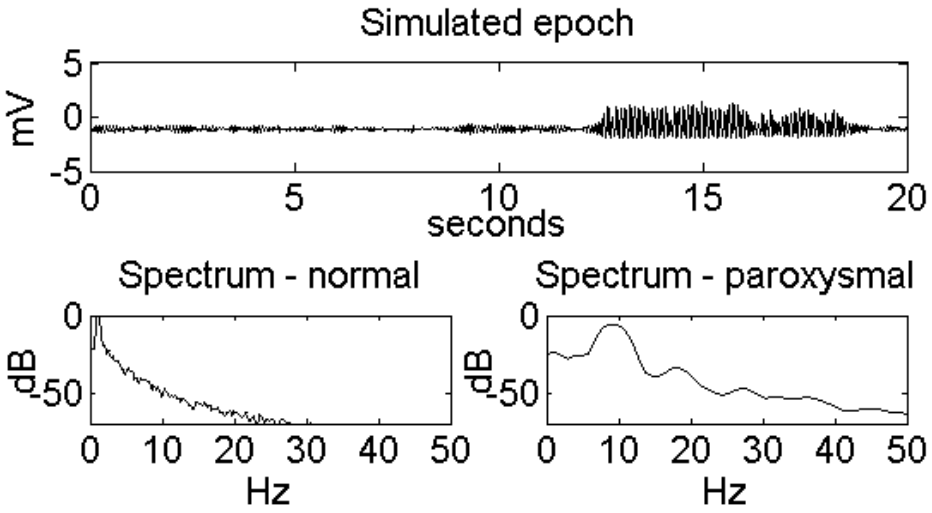
Clinical Presentation:
Distinct high-amplitude, bilateral synchronous, symmetric, 3 – 4 Hz spike-and-wave discharges of absence seizure.

Childhood Absence Epilepsy



Models of Epilepsy: Animal and Computational





Animal Models of Epilepsy

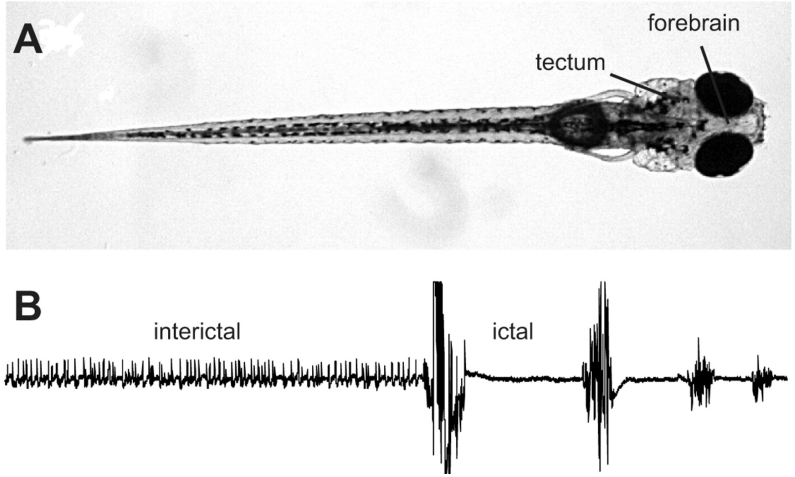
Species	*Drosophila melanogaster (fruit fly)*	*Danio rerio (zebra fish)*	*Mus musculus (mouse)*	*Canis familiaris (dog)*	*Papio hamadryas (baboon)*
First epilepsy studies	Dynamin mutant	Pentylene-tetrazole	Audio-genic	Electro convulsive	Photosensitive
Number of neurons	100,000	100,000 (larvae)	71,000,000	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:

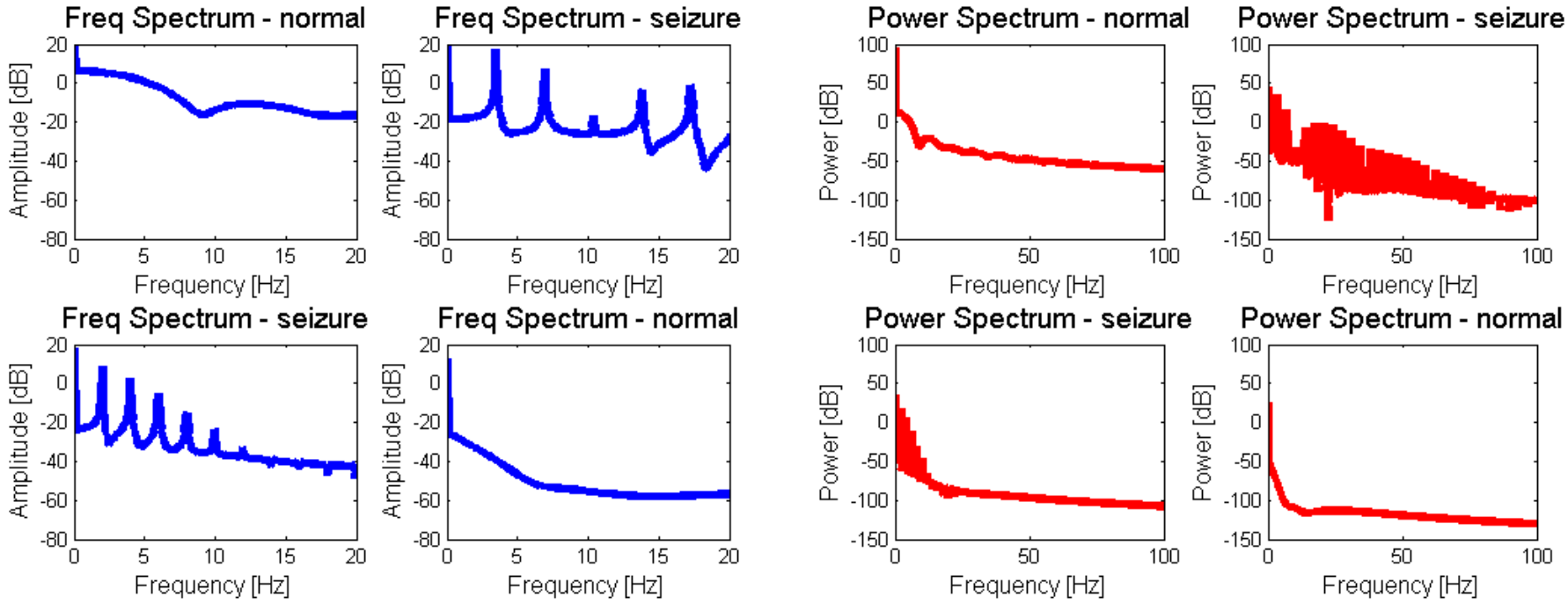
- Knockdown of genes
- SCN1A Mutants

Non-Genetic Models of Seizures:

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



Computational Model of Absence Epilepsy



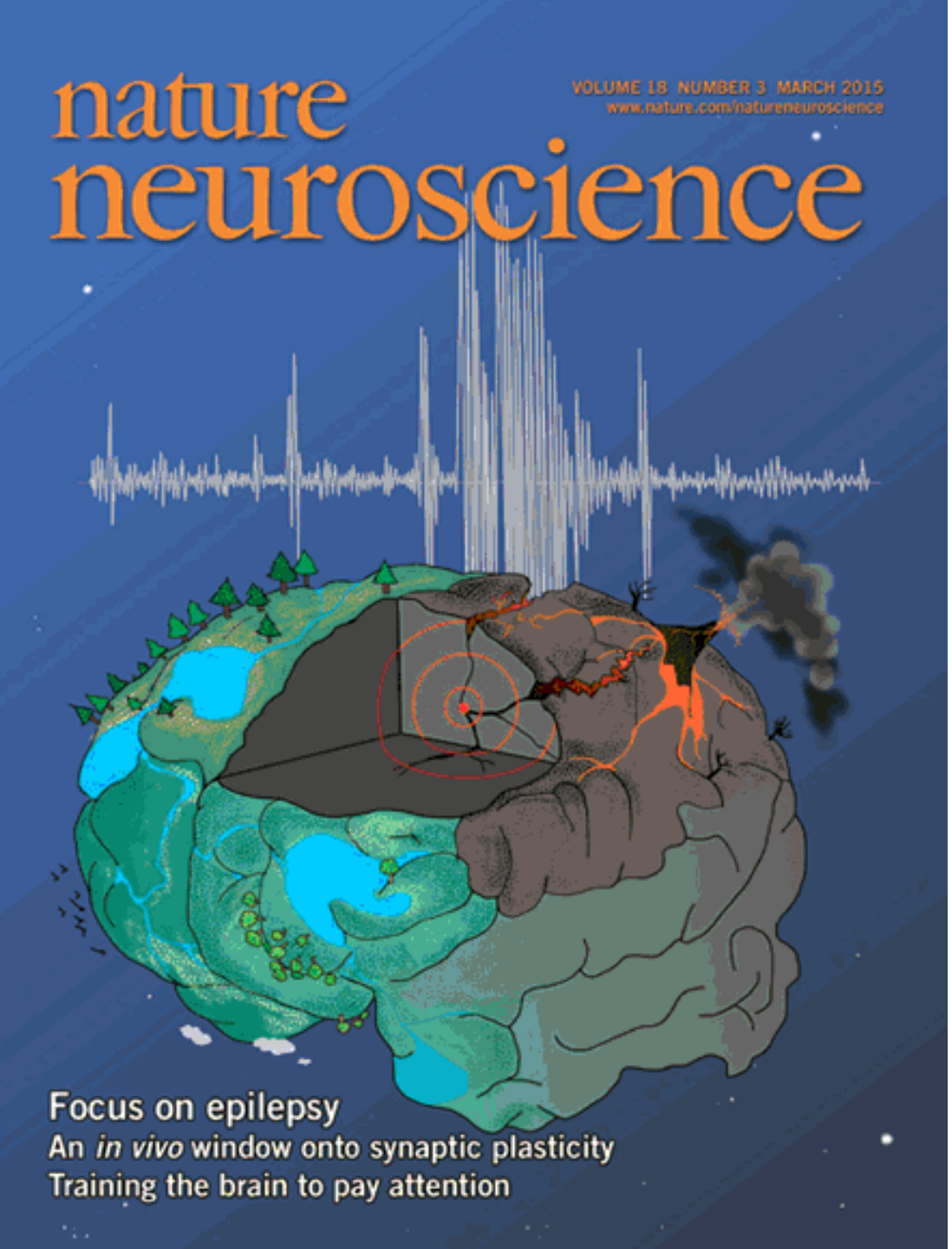
On Left: Frequency Spectrum of Epilepsy Simulation

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**



Epilepsy: disorder of brain dynamics

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

Current Treatment:

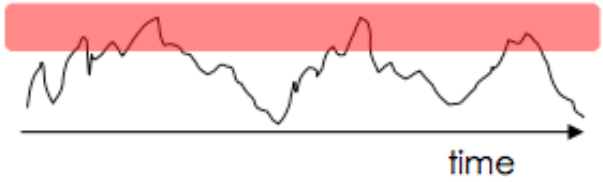
- Anti-Epileptic Drugs *(undesirable side effects)*
- Surgical Removal of Tissue

Motivation for Seizure Prediction:

- Increase quality of life of epilepsy sufferers

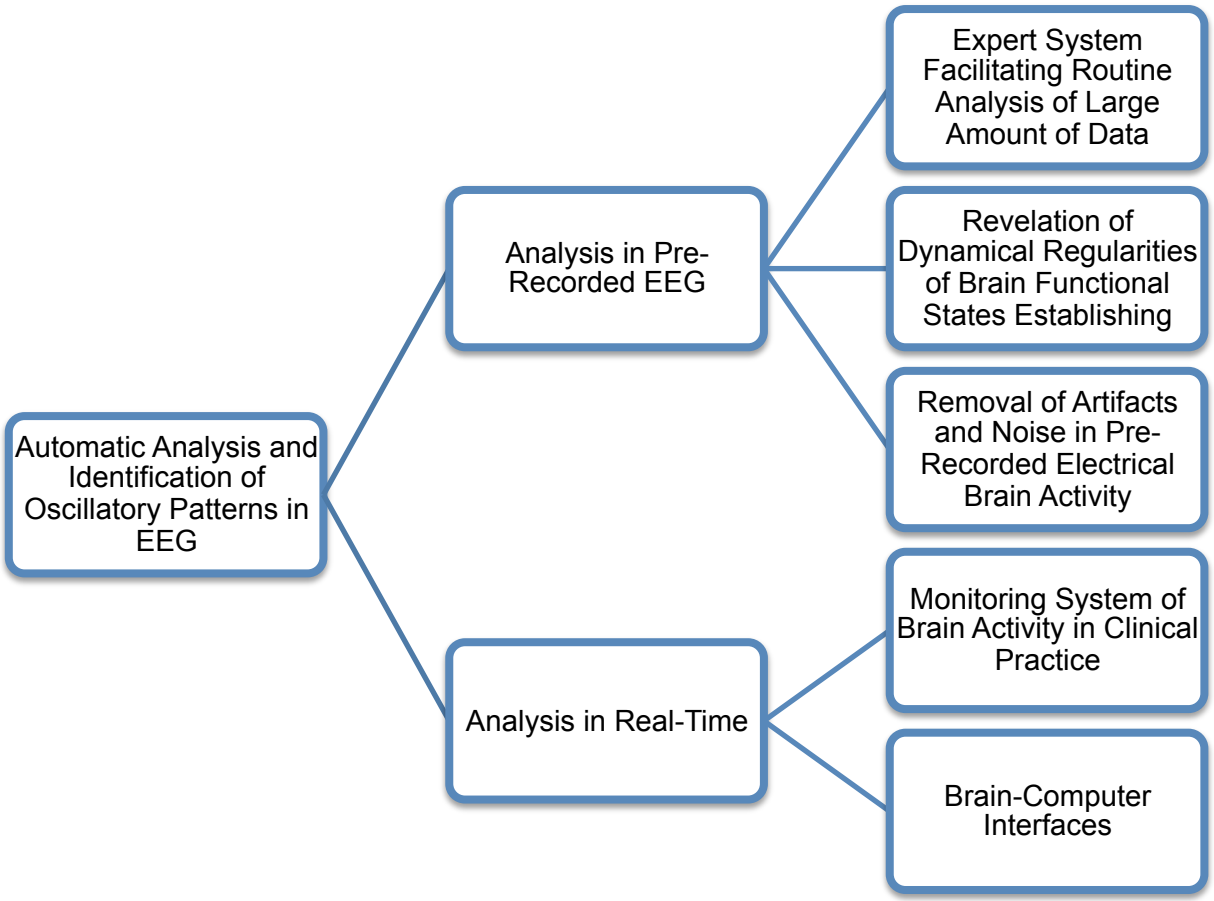
A robust seizure prediction algorithm requires ***machine learning.***

Approaches to the problem

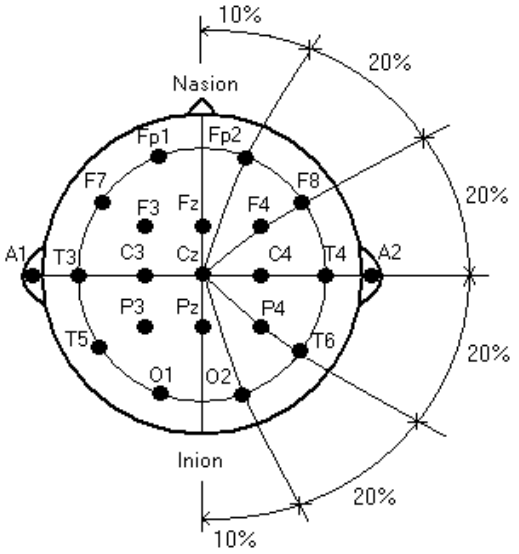
Feature extraction from EEG:	**Relationship** between EEG channels:	**Classification** based on:
Linear *System of noise-driven linear equations* $y(t) = ax(t) + b + \eta(t)$	**Univariate** *1 channel at a time*	**Statistics** *Discriminating measure* 
Non-linear *Deterministic dynamical system of nonlinear equations*	**Bivariate** *Varying synchronization of EEG channels* 	**Algorithm** *Machine Learning: neural networks, genetic optimization…*

Slide by Yann LeCunn

Analysis of Electroencephalogram (EEG) Data



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

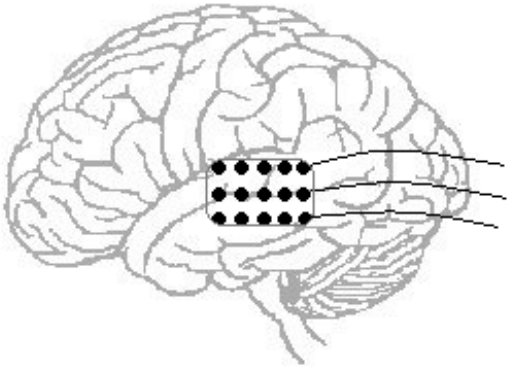


Flowchart: Review of methods available for EEG analysis

<u>On Right:</u>

Top: Scalp EEG data

Bottom: Intracranial grid EEG data



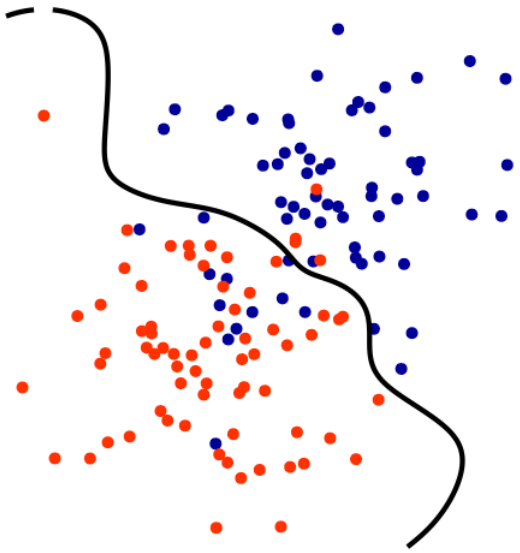
The Seizure Prediction Problem

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)

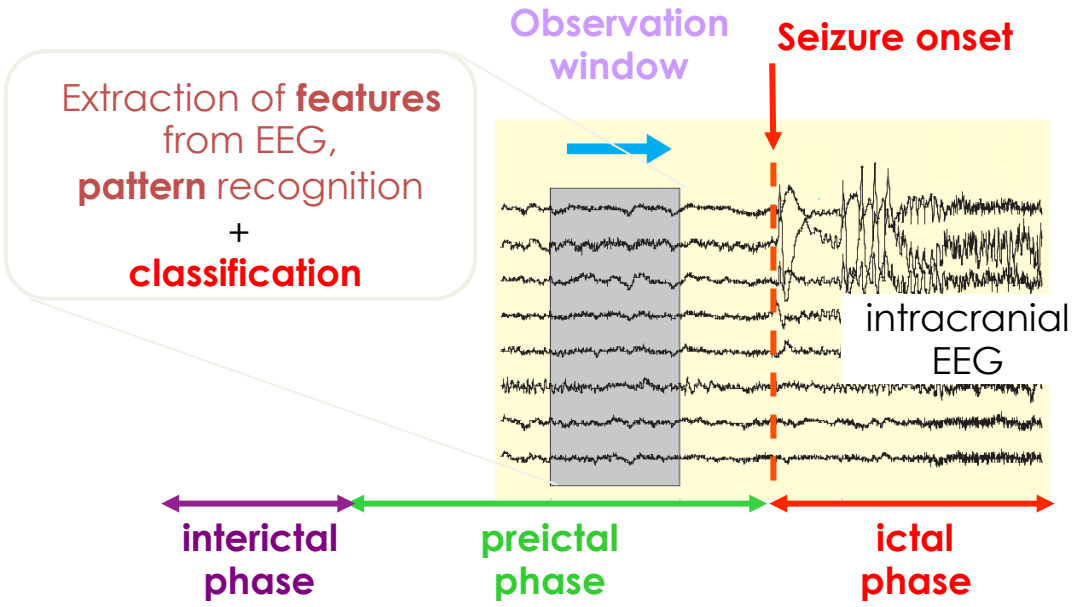


A decision boundary is the region of a problem space in which the output label of a classifier is ambiguous.

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)

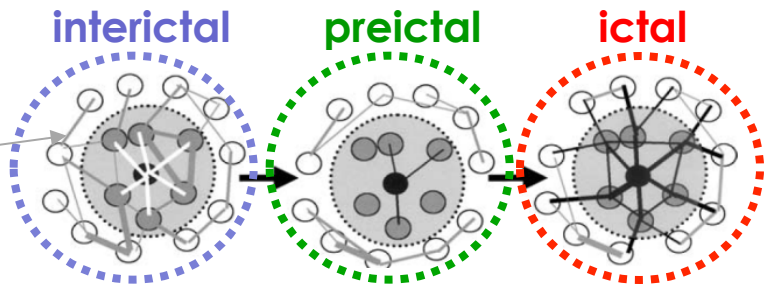


Hypotheses

- 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



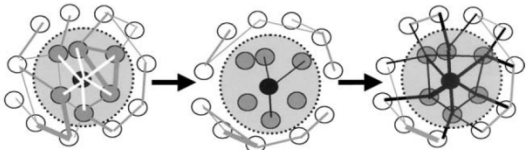
- goal: **patient-specific automatic learning to differentiate preictal and interictal patterns of brainwave synchronization features**

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

Slide by Yann LeCunn

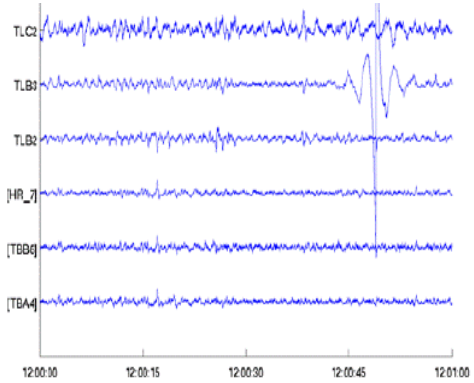
Patterns of bivariate features

Varying synchronization of EEG channels

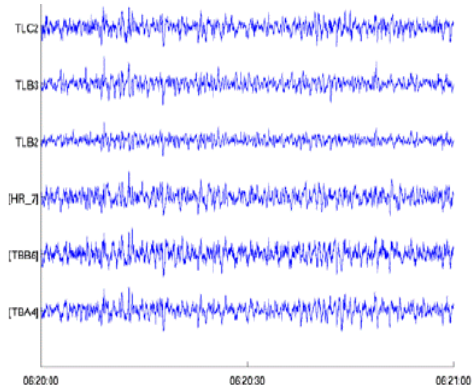


- Non-frequential features:
  - Max cross-correlation
    [Mormann et al, 2005]
  - Nonlinear interdependence
    [Arhnold et al, 1999]
  - Dynamical entrainment
    [Iasemidis et al, 2005]
- Frequency-specific features:
  [Le Van Quyen et al, 2005]
  - Phase locking synchrony
  - Entropy of phase difference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

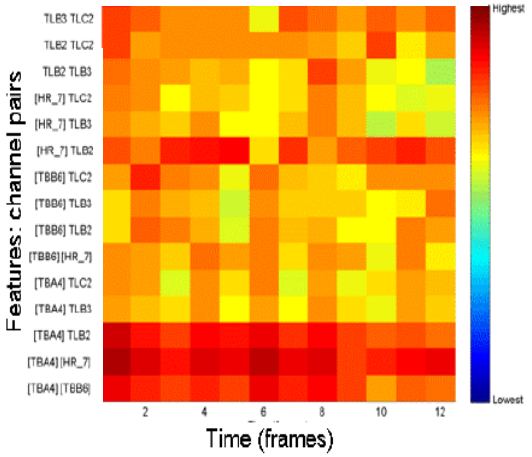
1min of interictal EEG



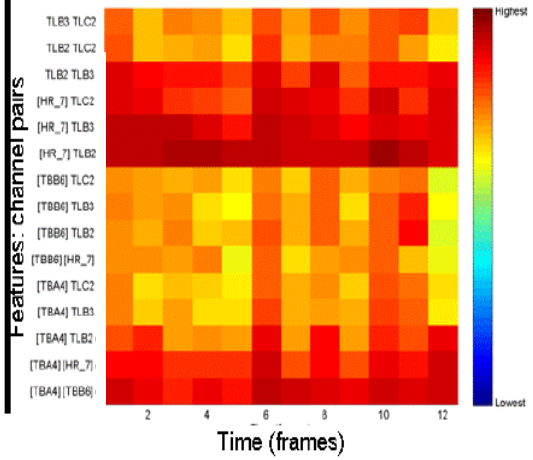
1min of preictal EEG



1min interictal **pattern**



1min preictal **pattern**



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

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

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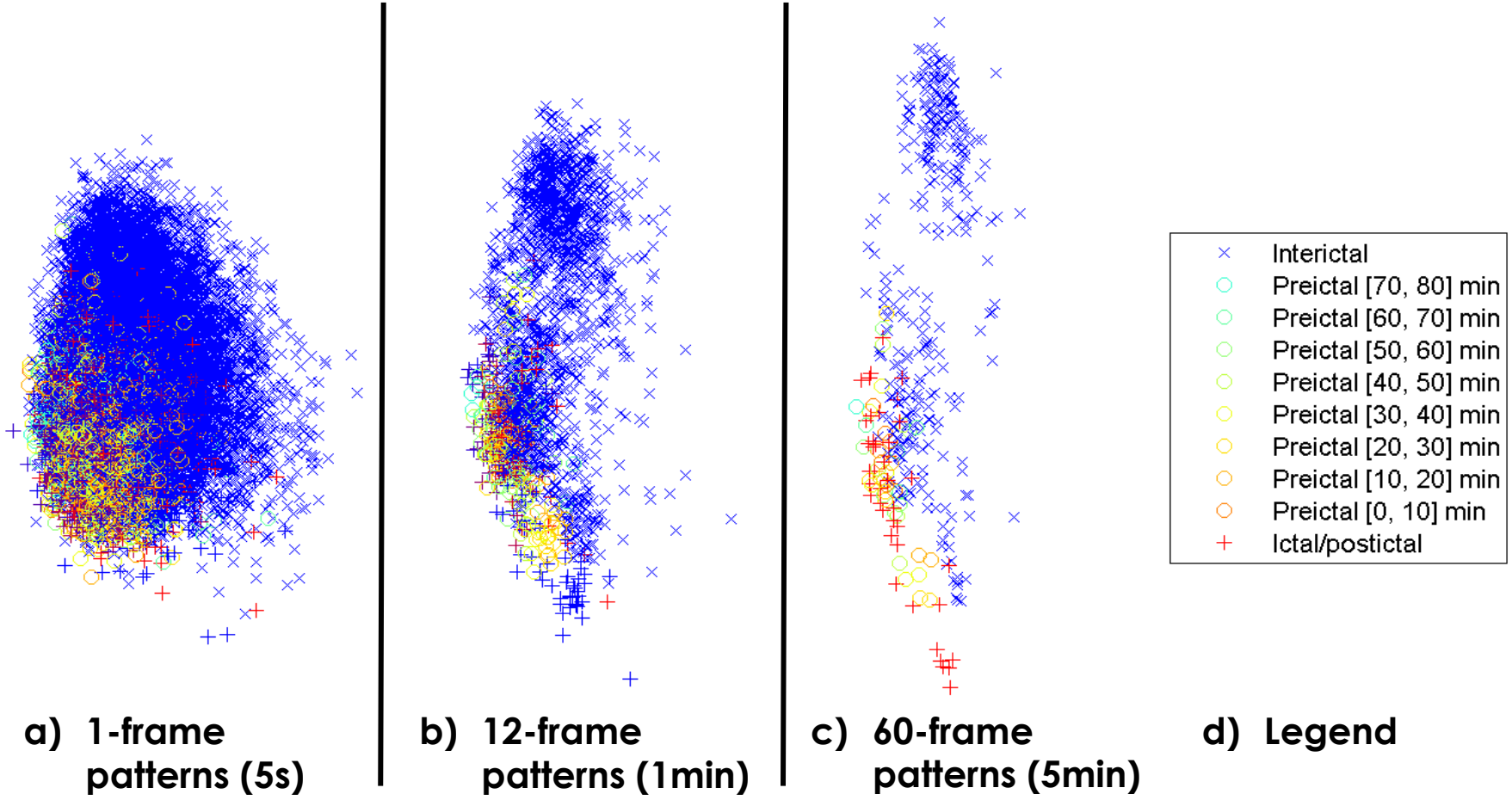
Separating patterns of features



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]

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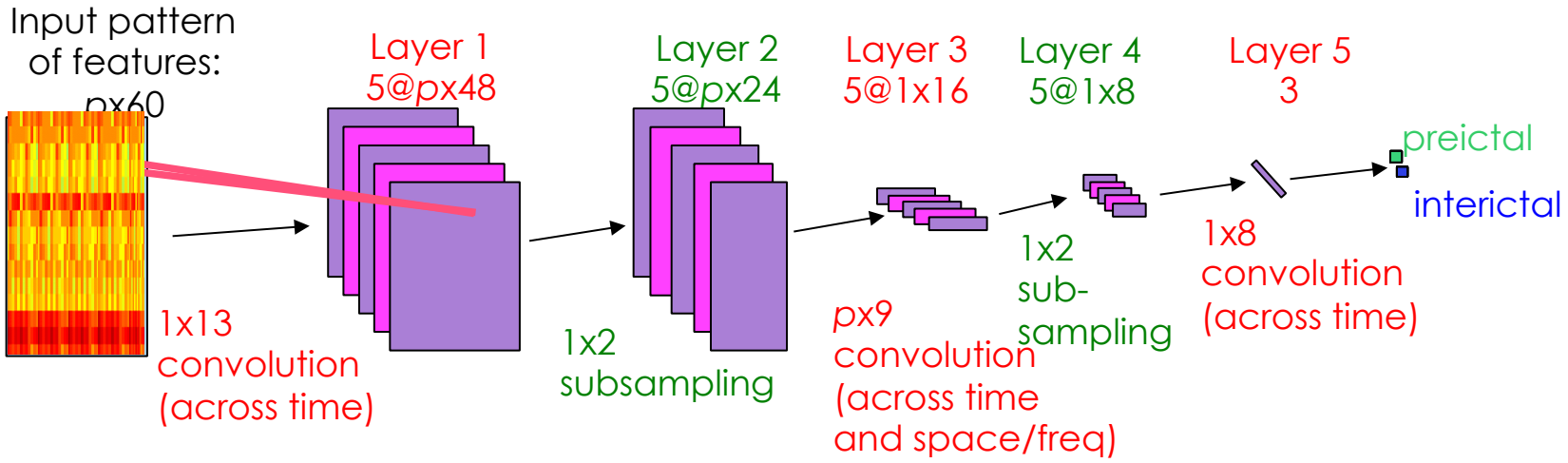
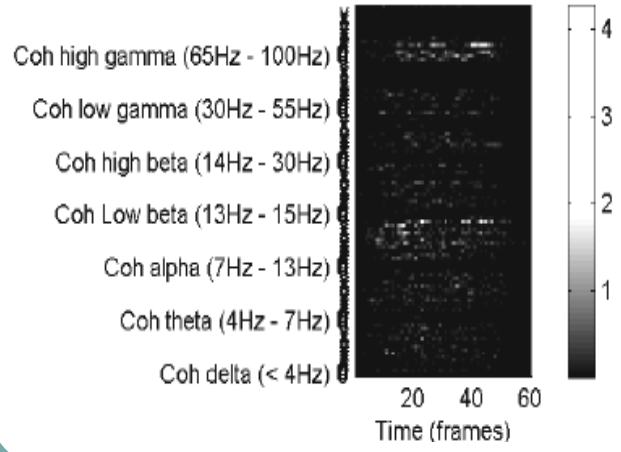
Machine Learning Classifiers



- 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]

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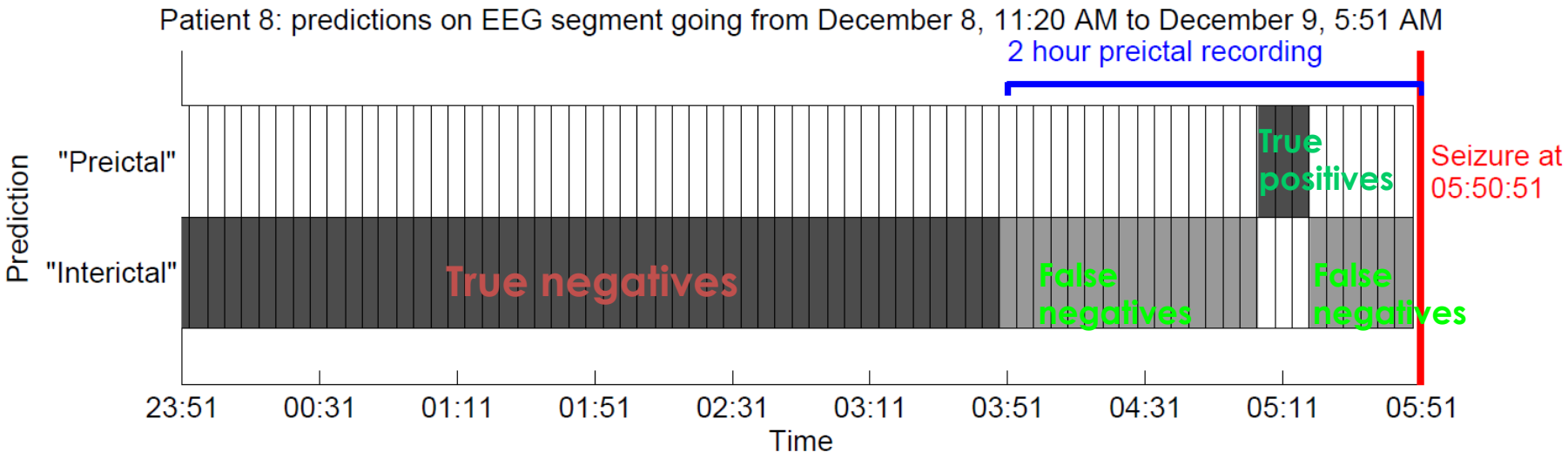
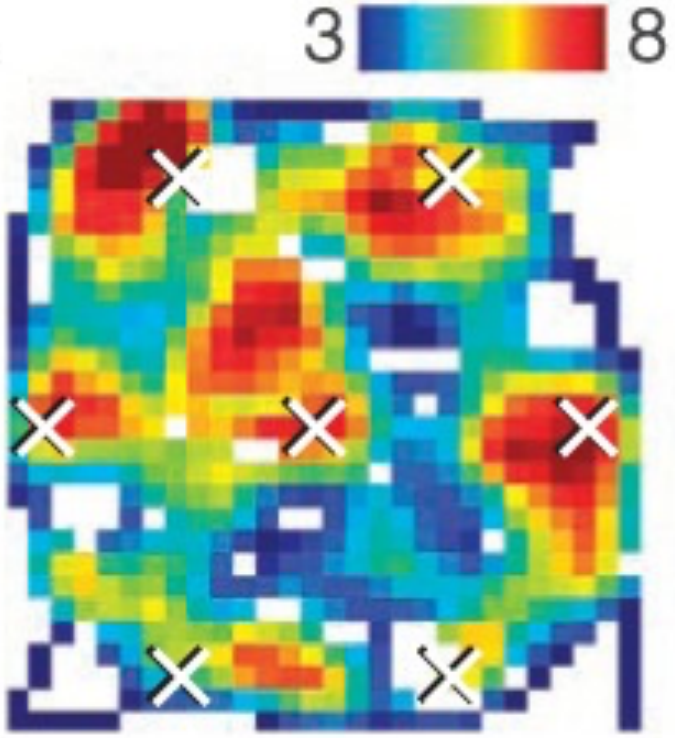
Example of Seizure Prediction

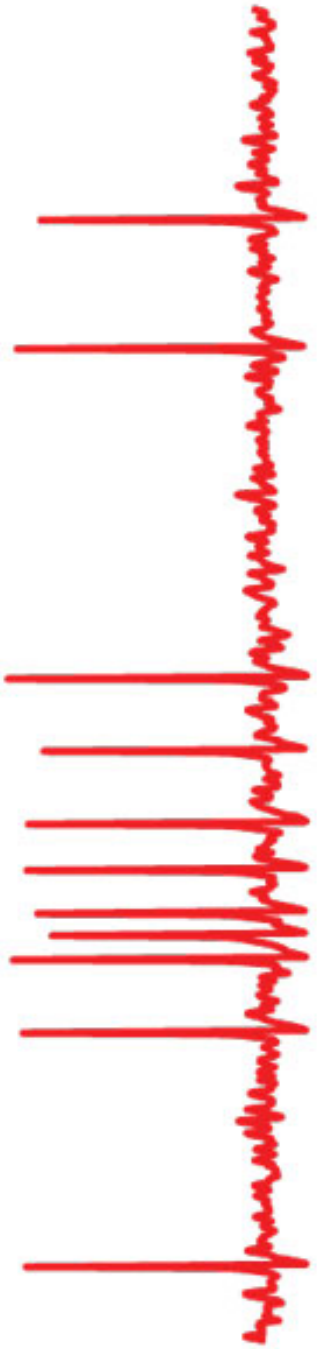


	Hypothesis: Patient has seizure.	**Null Hypothesis: Patient does not have seizure.**
Reality: Patient does not have seizure.	Type I Error (model predicts seizure but patient does NOT have seizure) **False Positives**	Correct Outcome (model predicts no seizure and patient does NOT have seizure) **True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

Artificial Intelligence in Healthcare

Next Time:





Guest Lecture by Professor Joshua Jacobs

"Human Invasive Brain Recordings"

Department of Biomedical Engineering
Columbia University