

Epilepsy and Neural Engineering

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Overview

1. Epilepsy

- definition
- causes
- current research situation

2. Mechanism under Epilepsy

- neural circuits
- generation of epilepsy

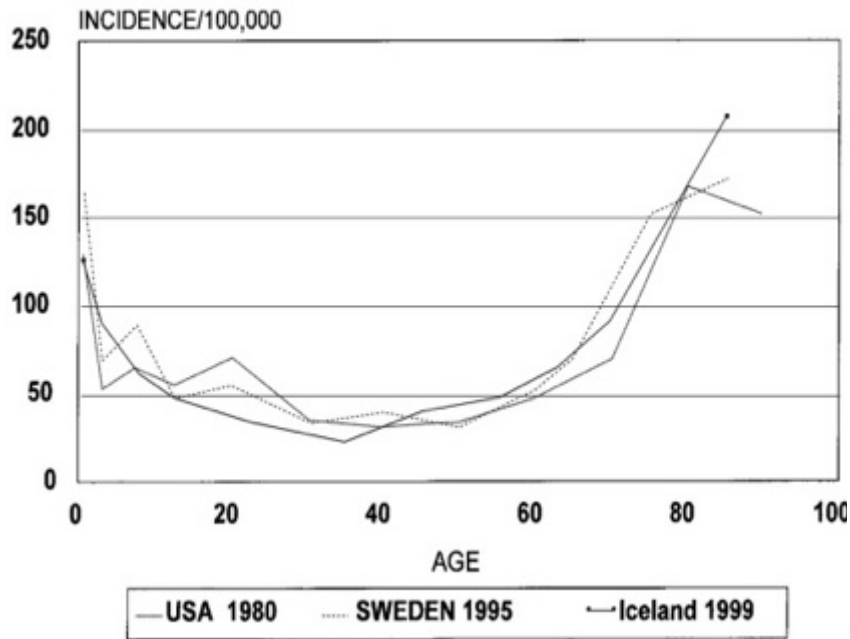
3. Developing Treatments for Epilepsy

- diagnostics
- electrical stimulation
- faster drug development

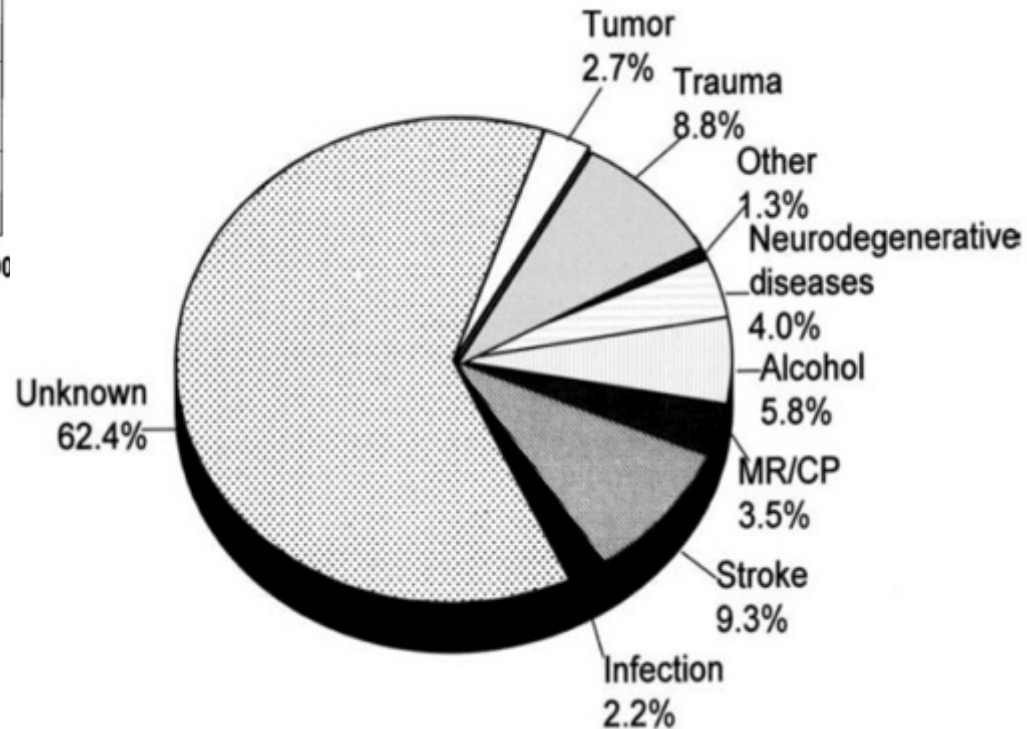
Epilepsy

-- repeated occurrence of unprovoked seizures

Age-specific incidence of epilepsy



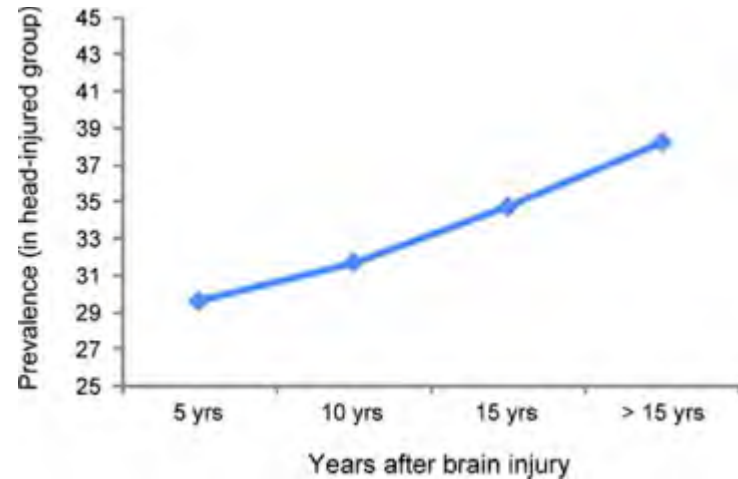
Causes of epilepsy



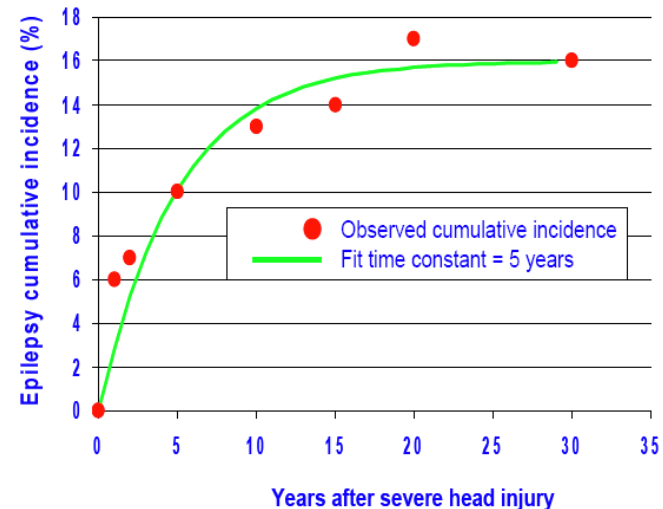
Posttraumatic Epilepsy-PTE



- Incidence after military head injury is up to **53%** of patients (Vietnam veterans)
- Incidence after civilian head injury - **17%**



Raymont V et al. Neurology 2010;75:224-229



Annegers JF et al, *N Engl J Med* 1998

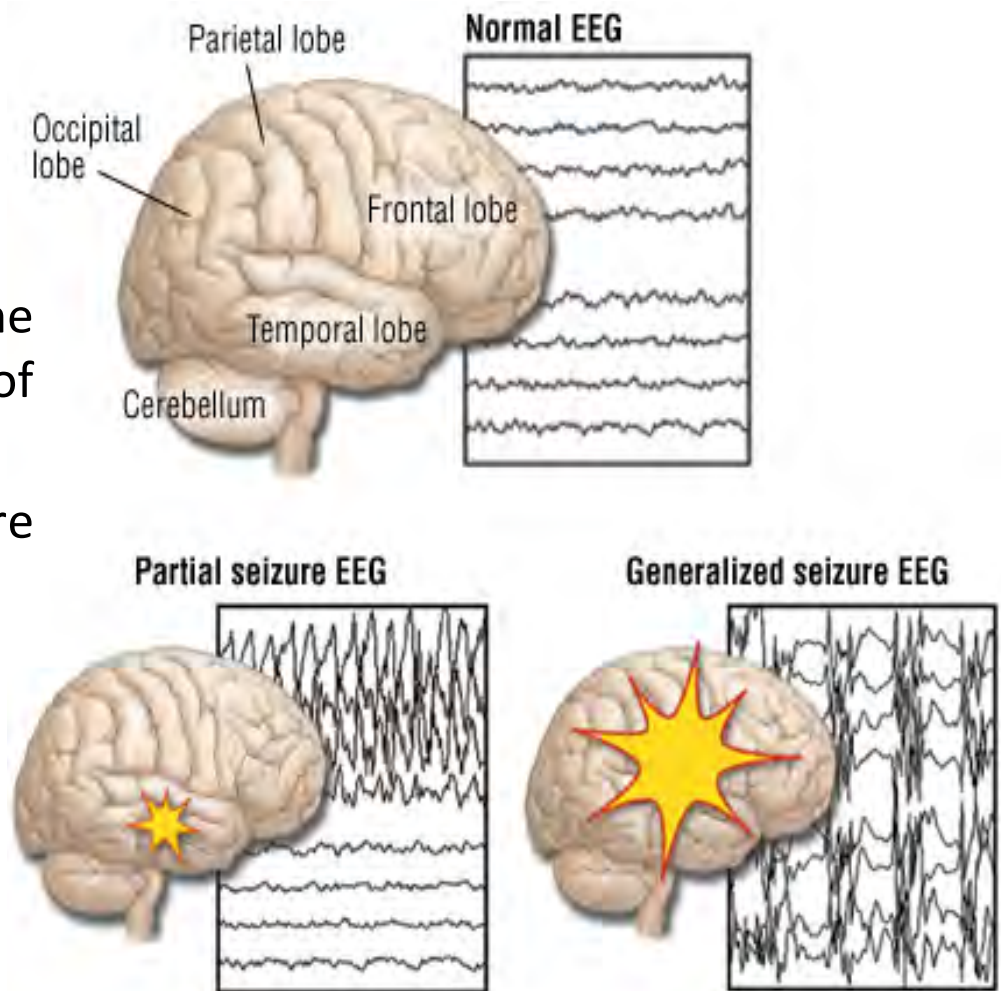
Facts about Epilepsy

- 1 – 3% of general population suffers from epilepsy (5-6 million people in US)
- In 70% of cases, epilepsy is controlled by antiepileptic medication
- Medications are not curative
- Anticonvulsants have side-effects
- In 30% of cases, epilepsy is not controlled by medication, or becomes drug-resistant. These patients may have to undergo surgery

Mechanism under Epilepsy/Seizure

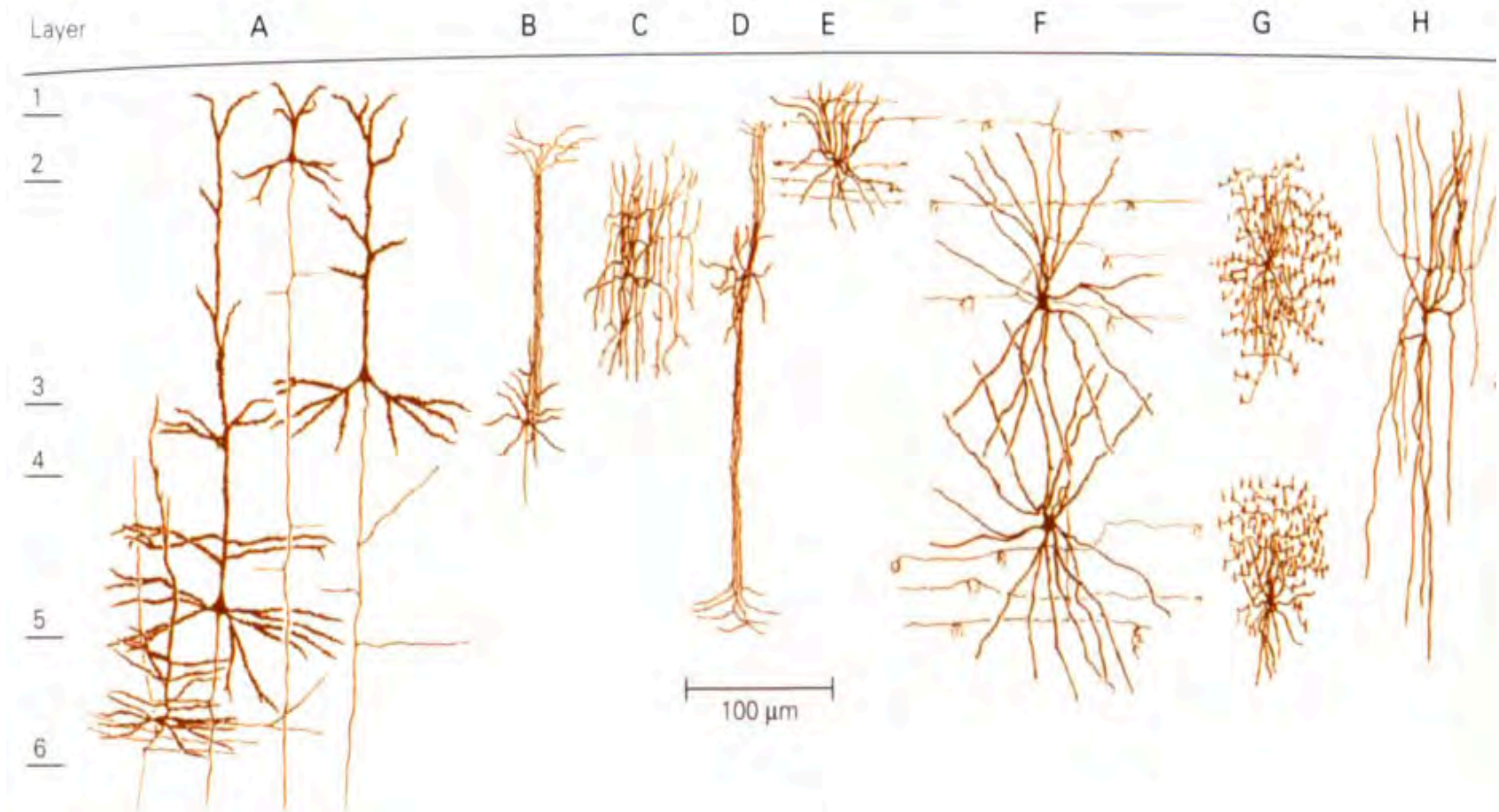
Classification:

1. A partial seizure begins in one brain area. It affects only part of the brain.
2. A primary generalized seizure involves the entire brain.



Mechanism under epilepsy

Neuronal Circuit

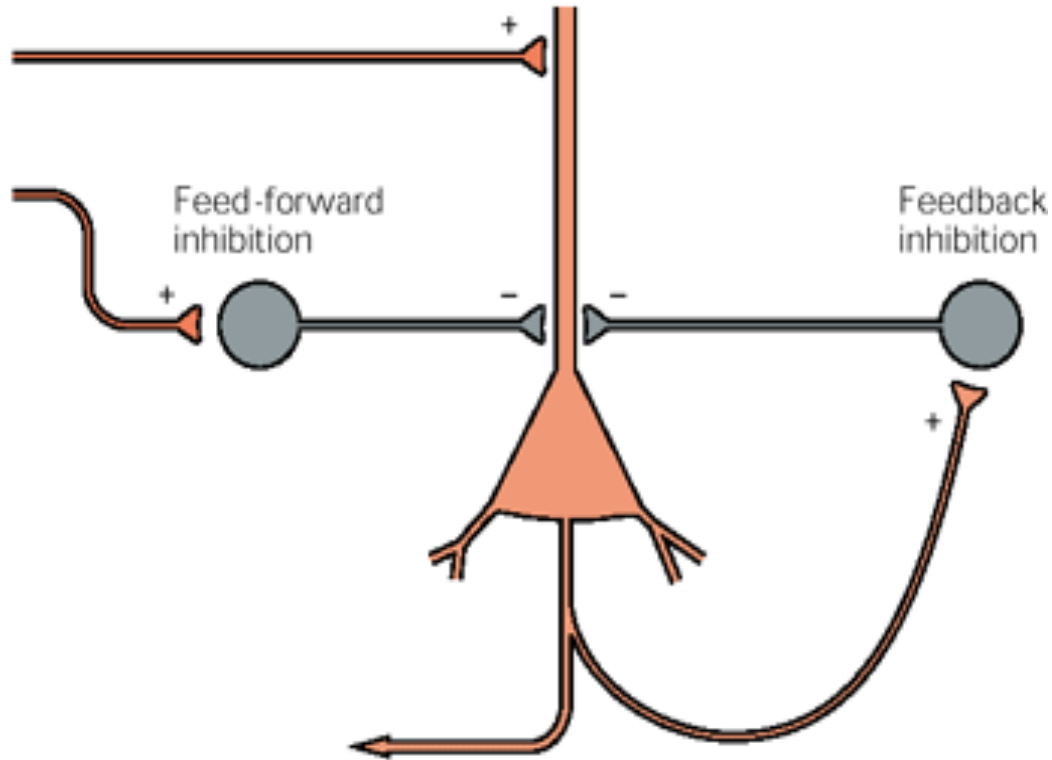


Excitatory neurons (A and B) – release excitatory neurotransmitter, cause other cells to activate

Inhibitory neurons (C-H) – release inhibitory neurotransmitter, cause other cells to de-activate

Mechanism under epilepsy

Neuronal Circuit

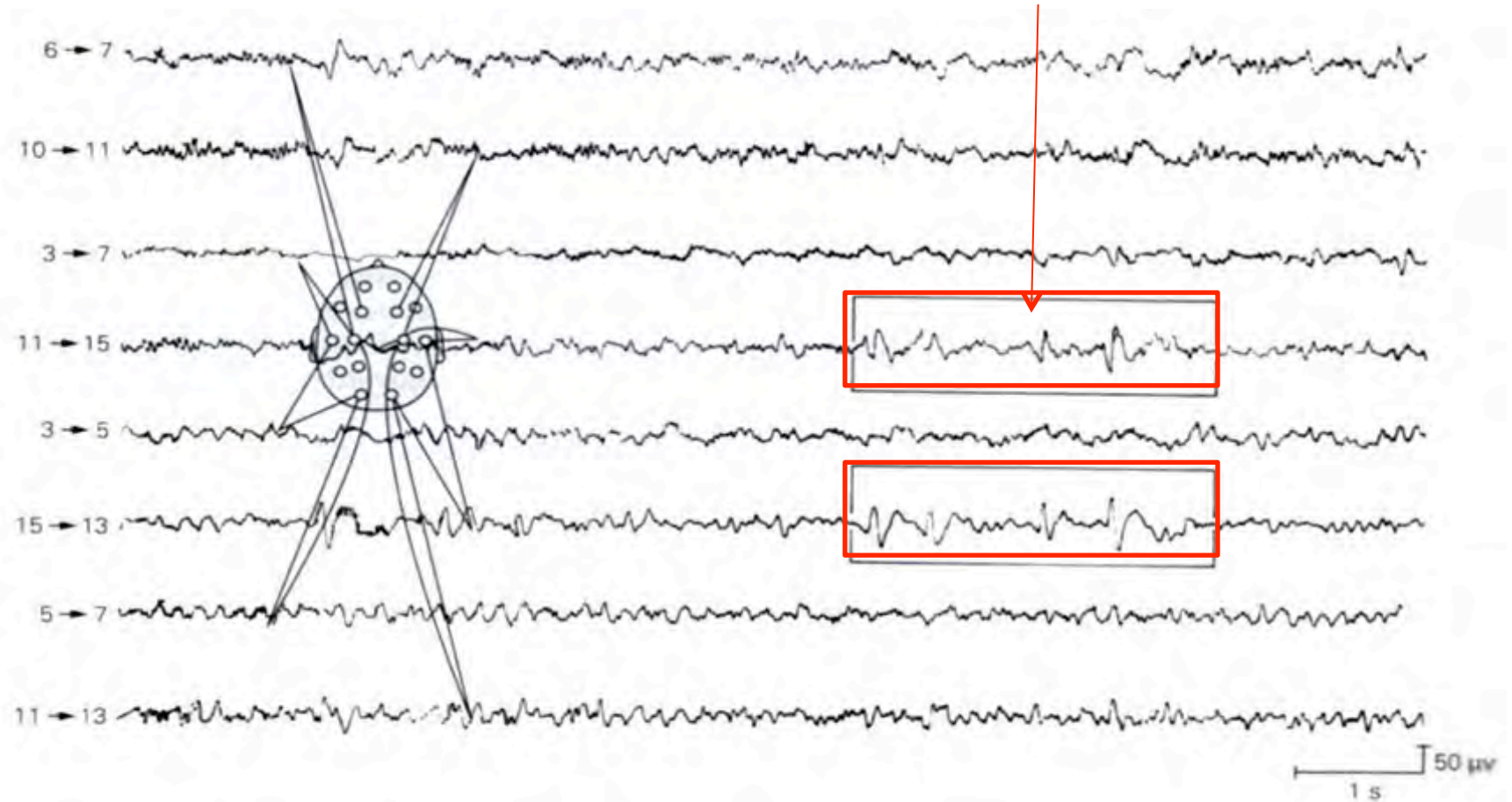


Basic cortical circuit

Generation of Seizures

Partial seizure

Interictal activity

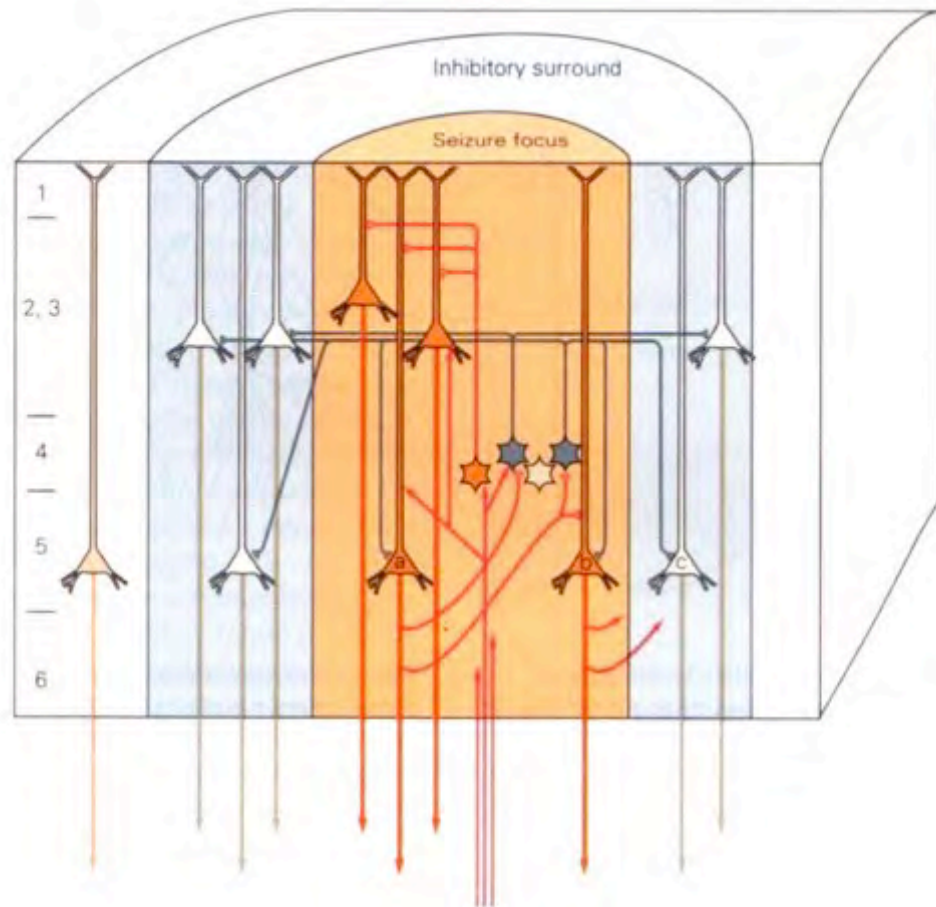


Partial Seizures Originate Within a Small Group of Neurons Known as a **Seizure Focus**

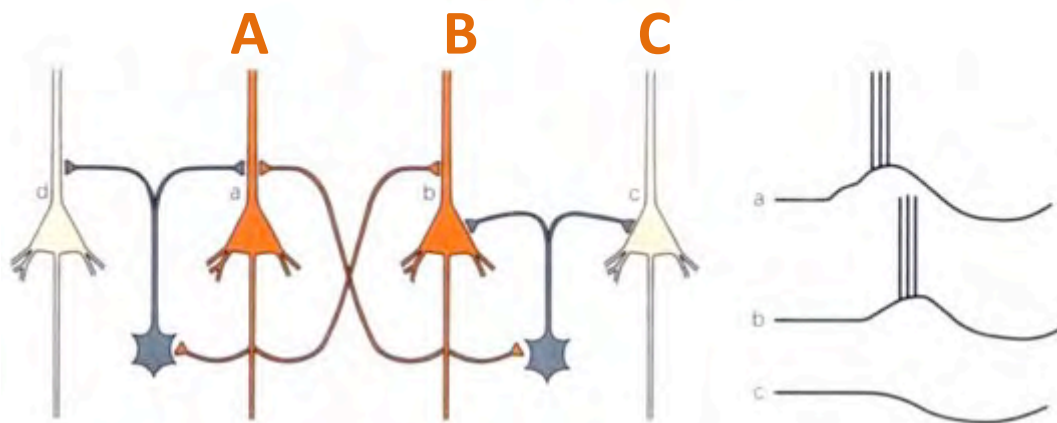
Generation of Seizures

Partial seizure

Interplay between excitation and inhibition in seizure focus



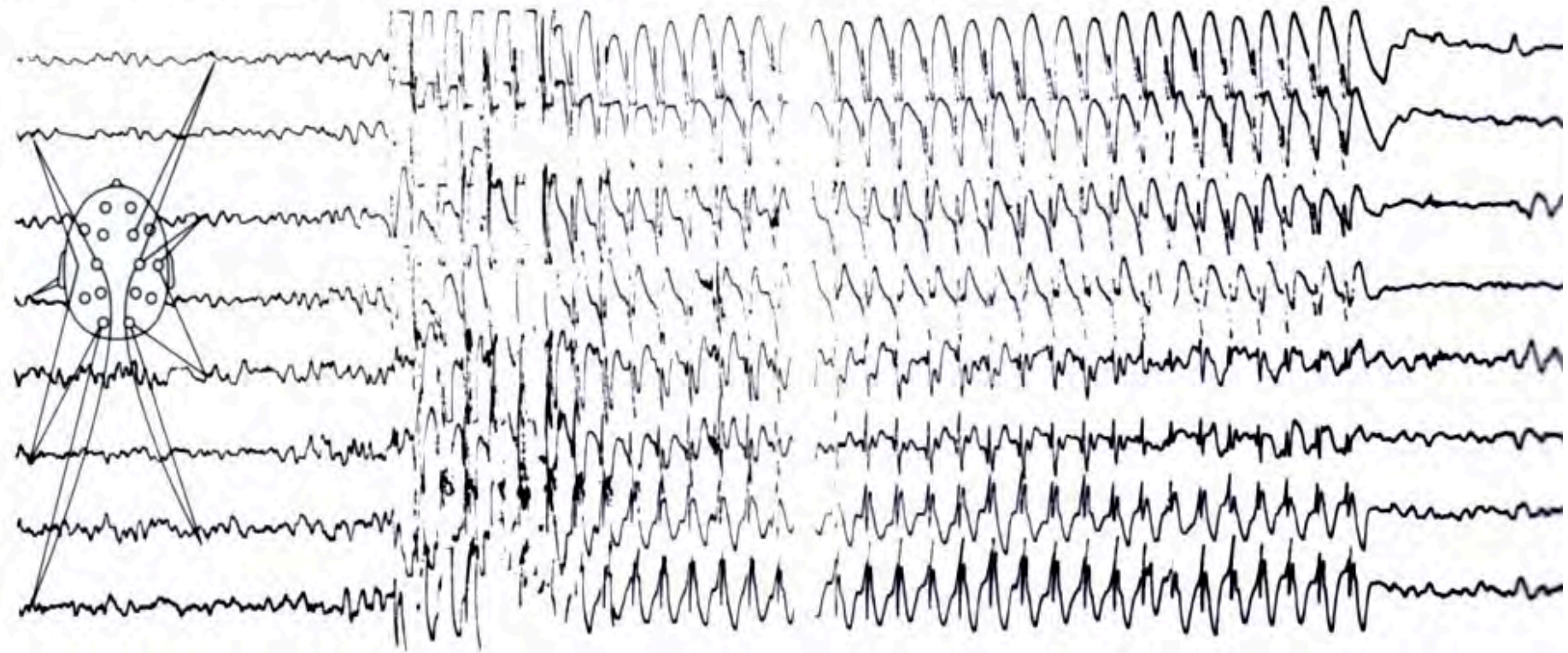
Seizure begins to spread beyond the original focus if **surround inhibition** breakdown



Generation of Seizures

Generalized Seizures

A Spike and wave activity in typical absence seizure

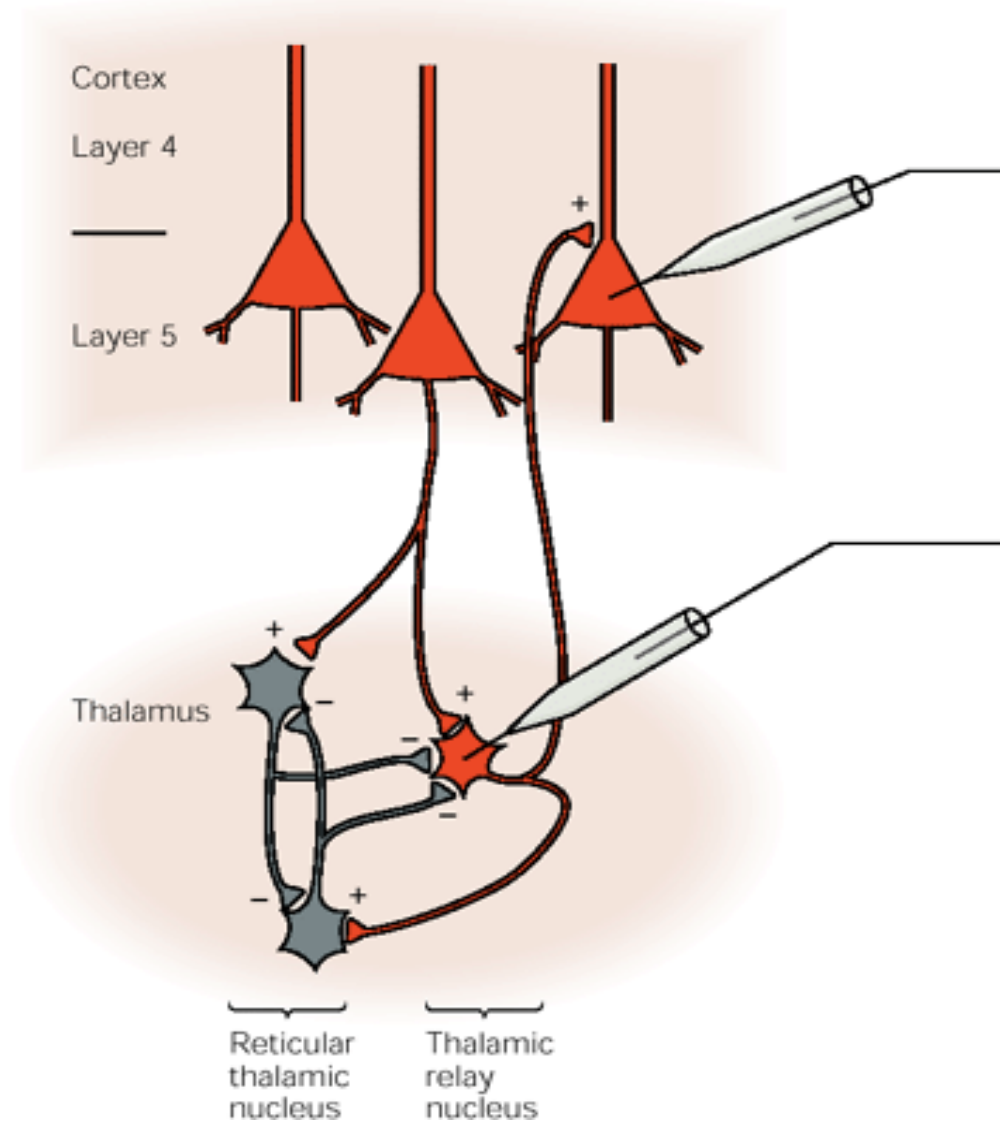


EEG from a 12-year-old patient with typical absence seizures

Generation of Seizures

Generalized Seizures

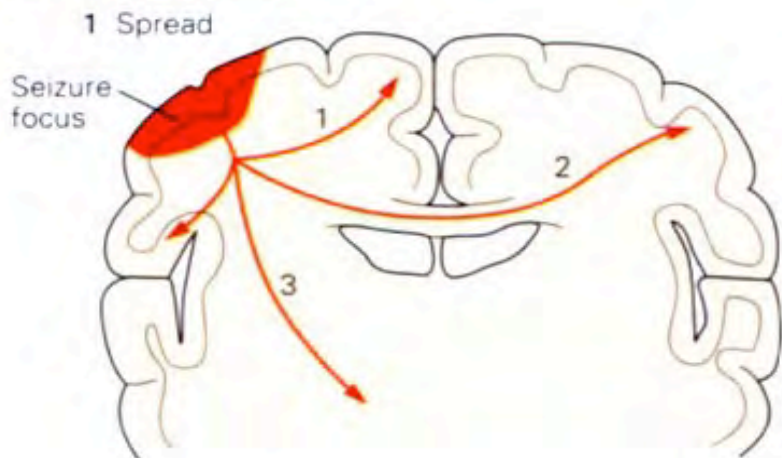
Generalized Seizures Evolve From
Thalamocortical Circuits



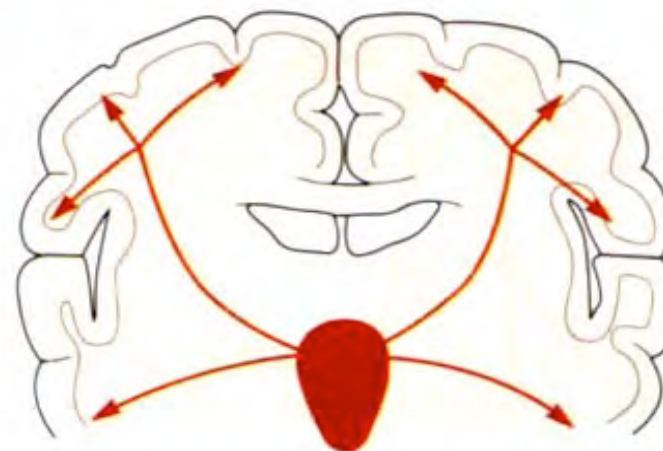
Mechanism under epilepsy

The pathways of seizure propagation

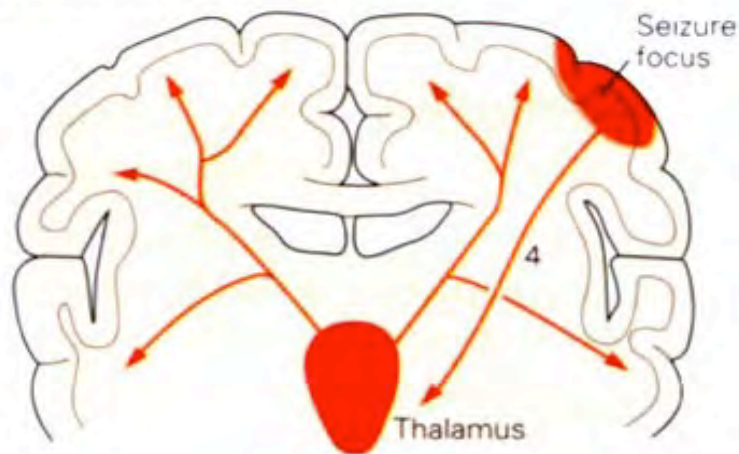
A Partial seizure



B Primary generalized seizure



2 Secondary generalization



A Clinical Case--Temporal lobe epilepsy

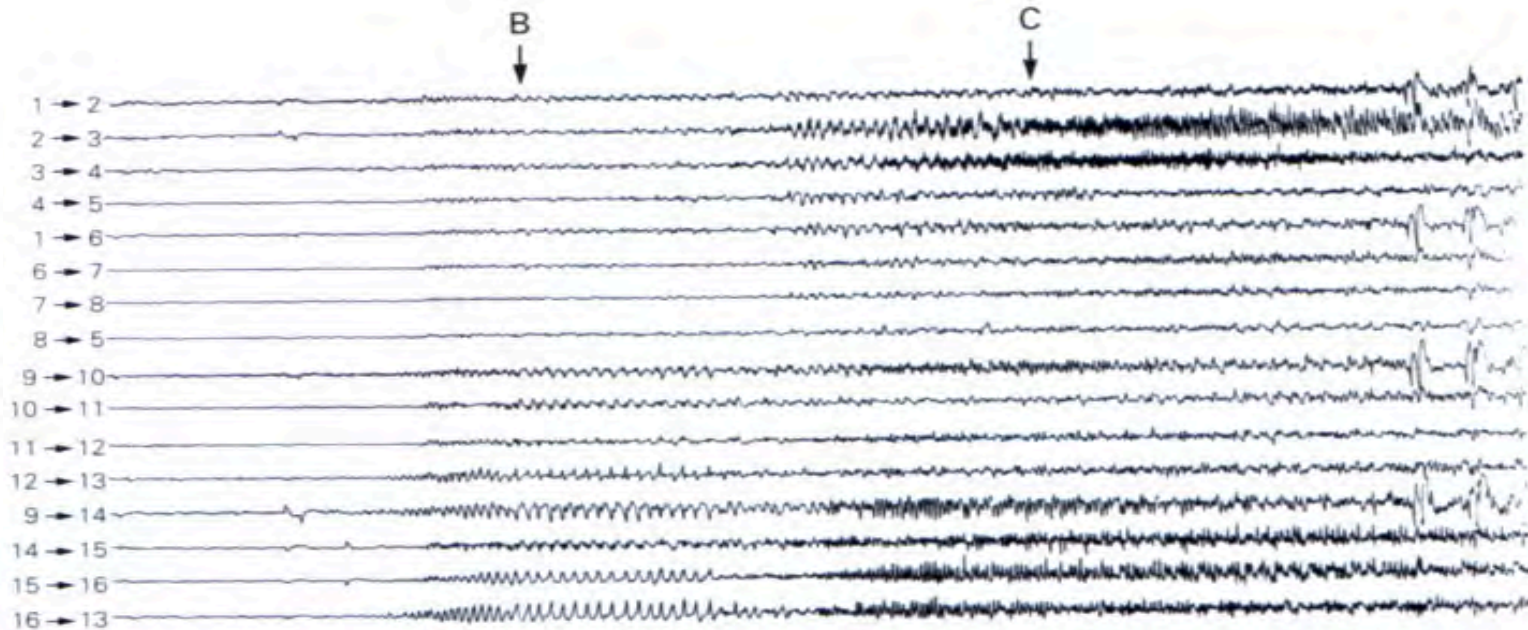
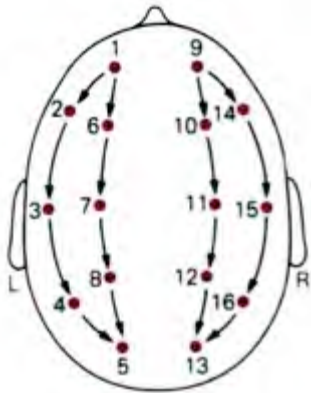
A. before seizure



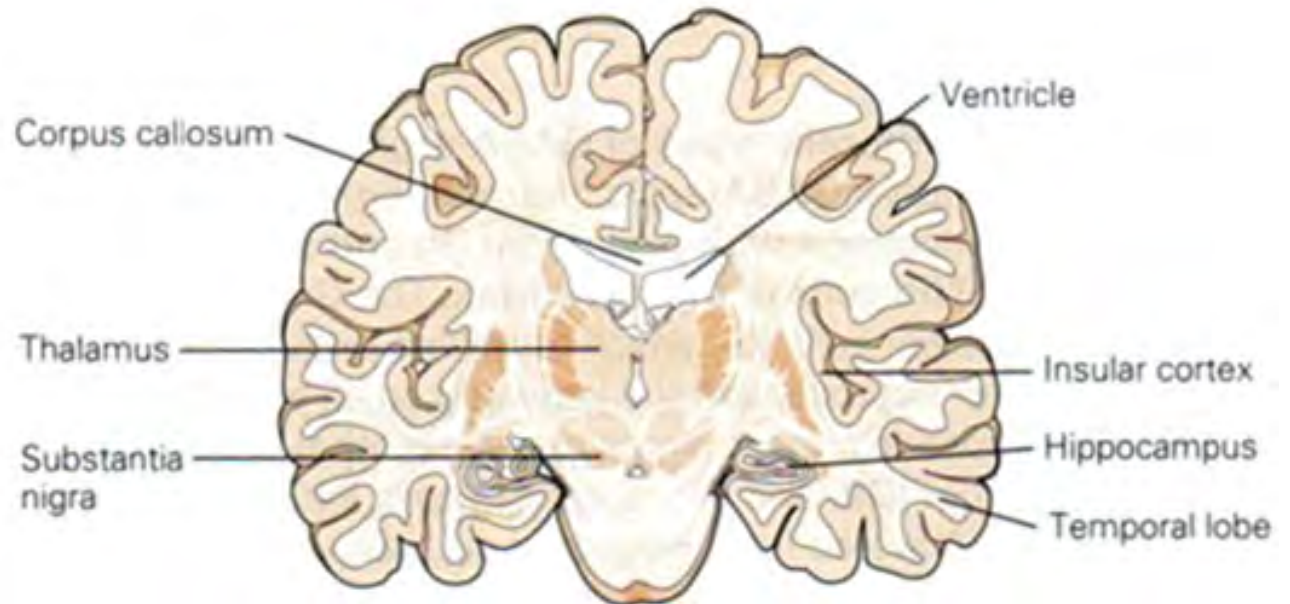
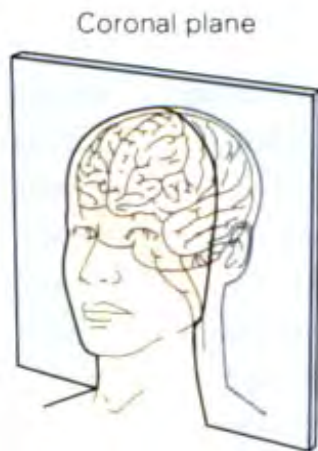
B. aura: feeling of fear



C. alteration of consciousness, screaming

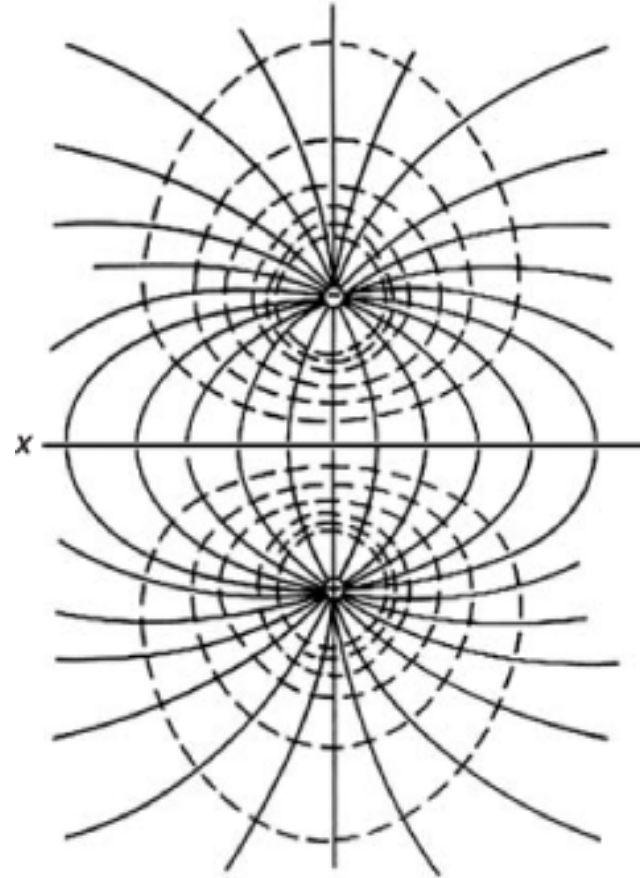
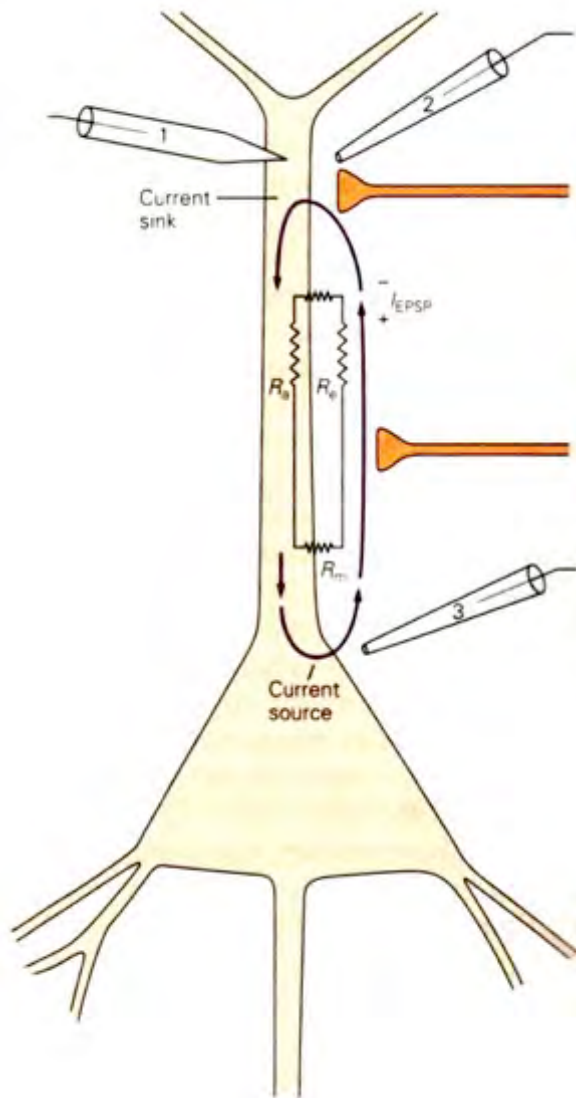


A Clinical Case--Surgical treatment of epilepsy



Developing treatments for Epilepsy

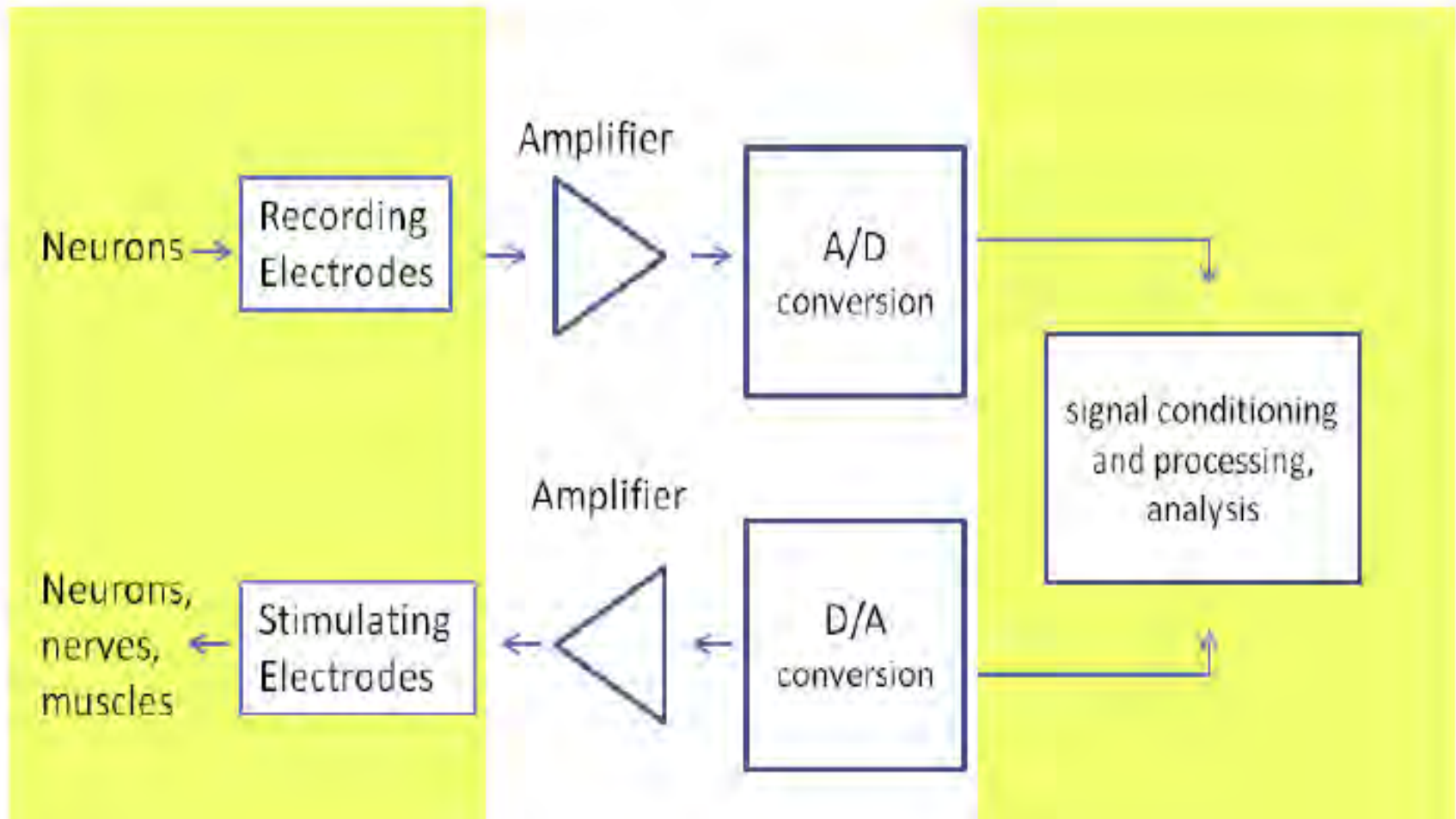
Interfacing Brain with Electrical System



- better diagnostics through electrode arrays
- stopping seizures with electrical stimulation
- faster drug development with brain-on-a-chip

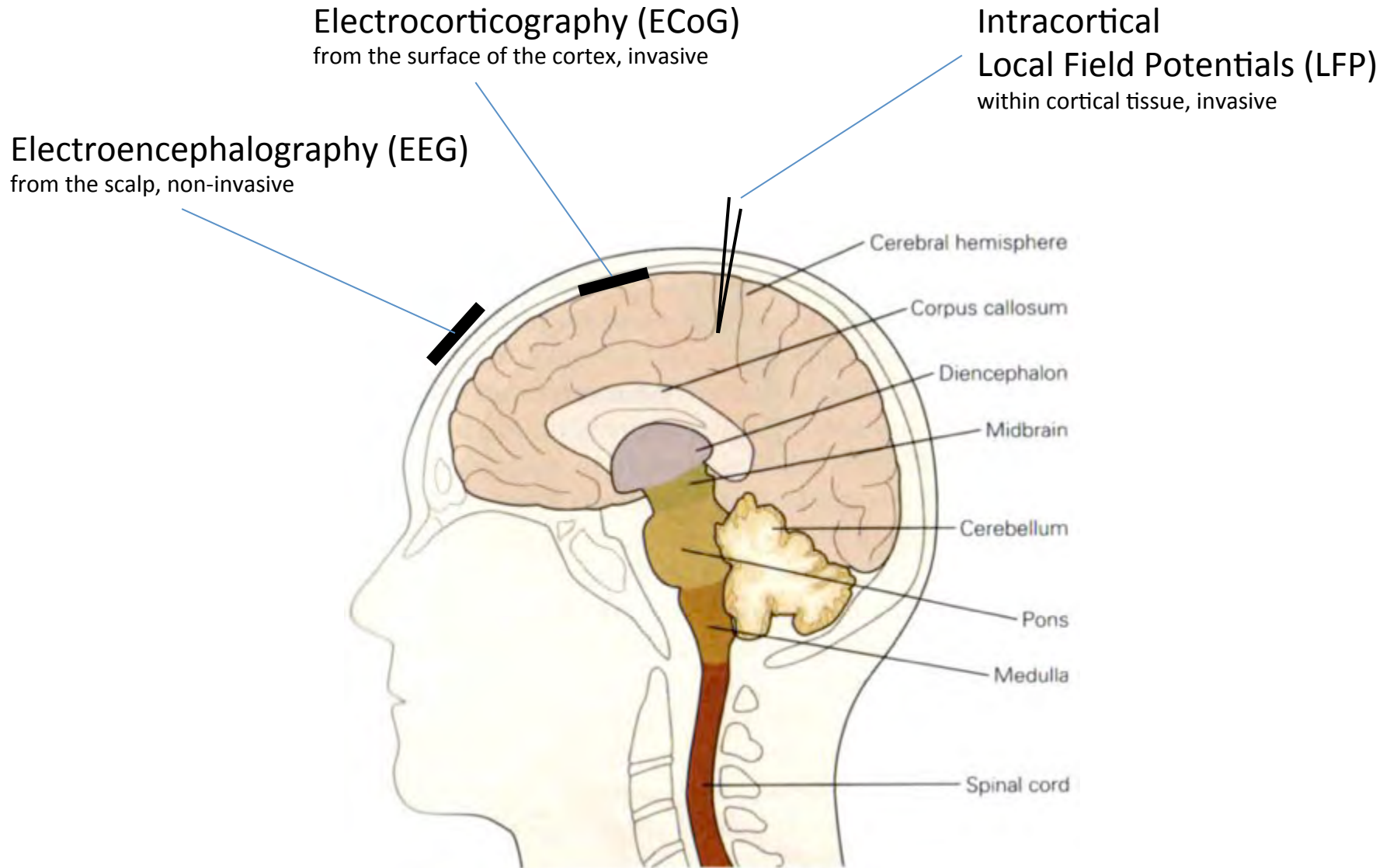
Developing treatments for Epilepsy

Interfacing Brain with Electrical System



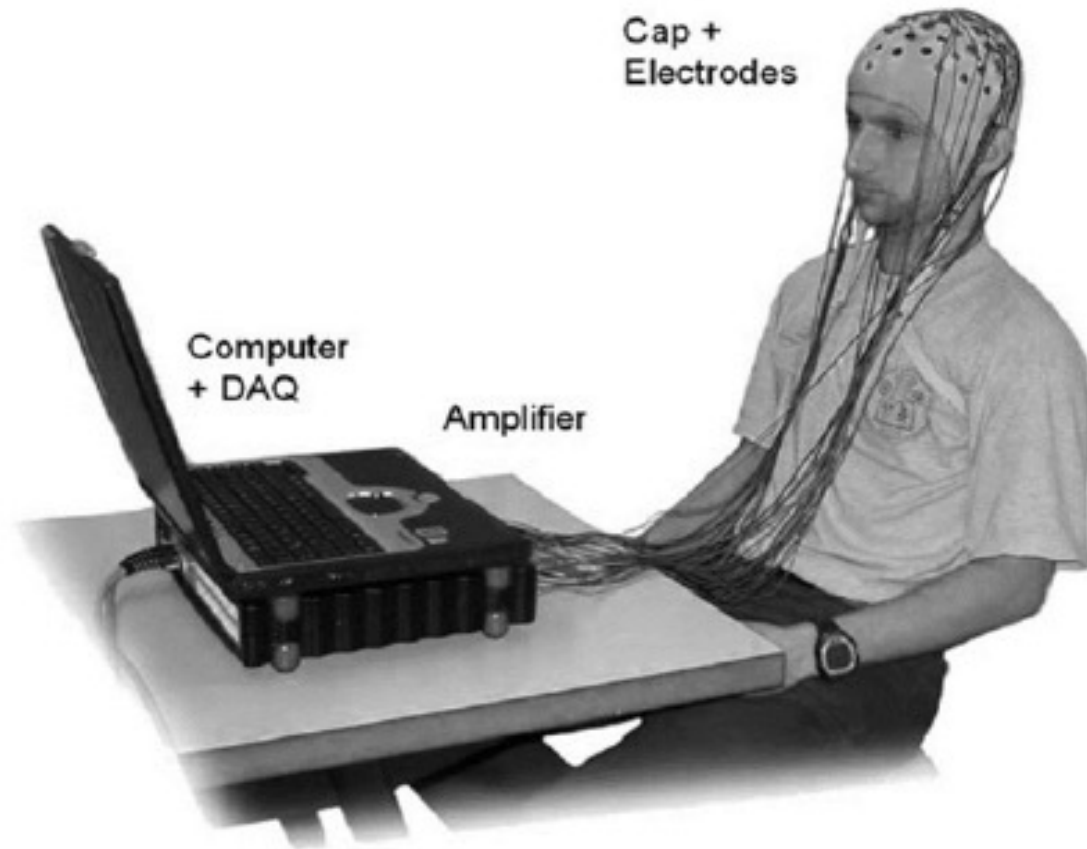
Developing treatments for Epilepsy

Diagnostics through Electrode Arrays



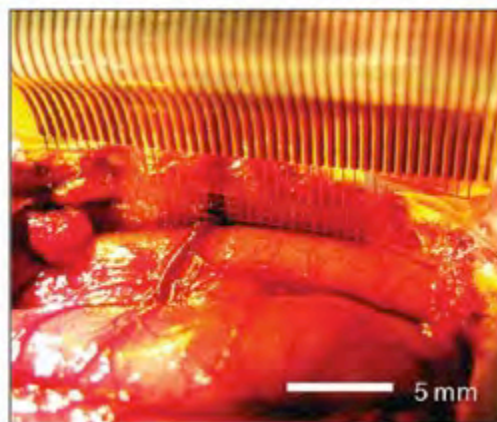
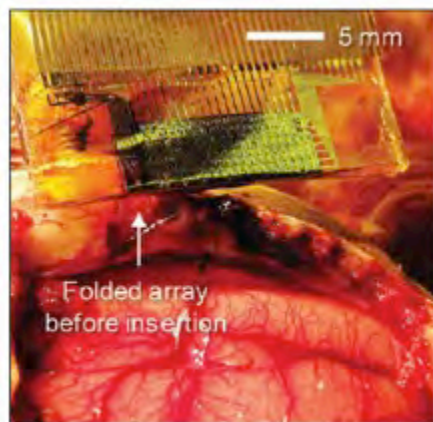
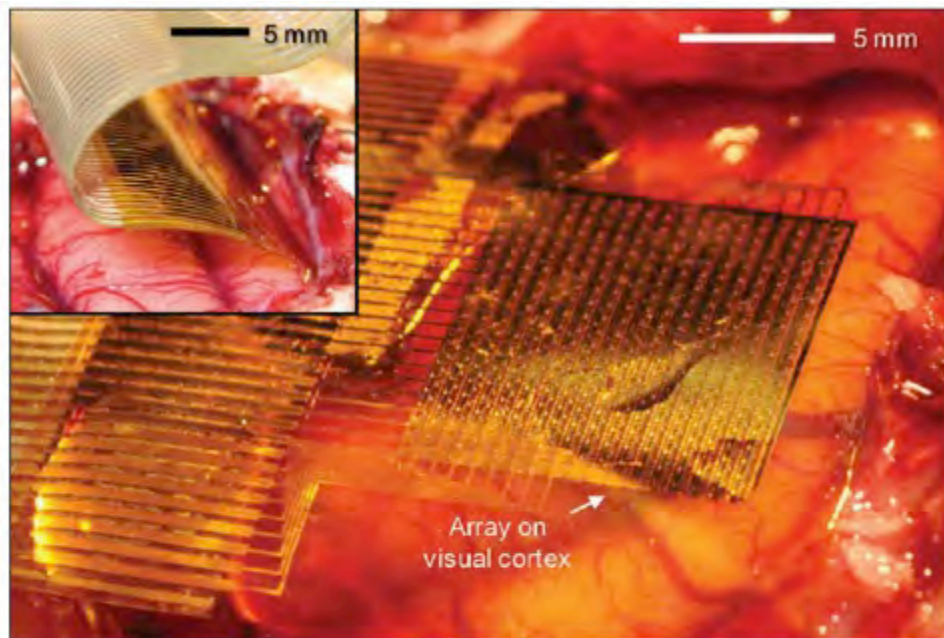
Diagnostics through Electrode Arrays

Electroencephalography (EEG)



Diagnostics through Electrode Arrays

Electrocorticography (ECoG)

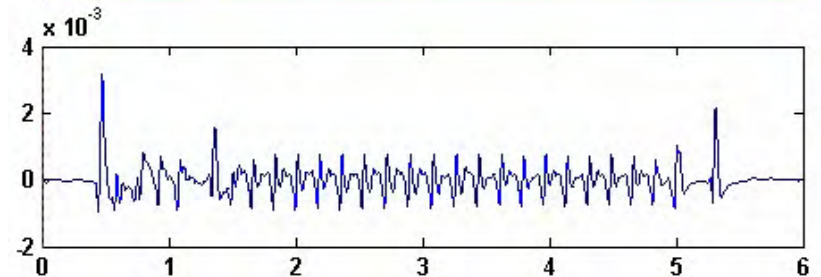
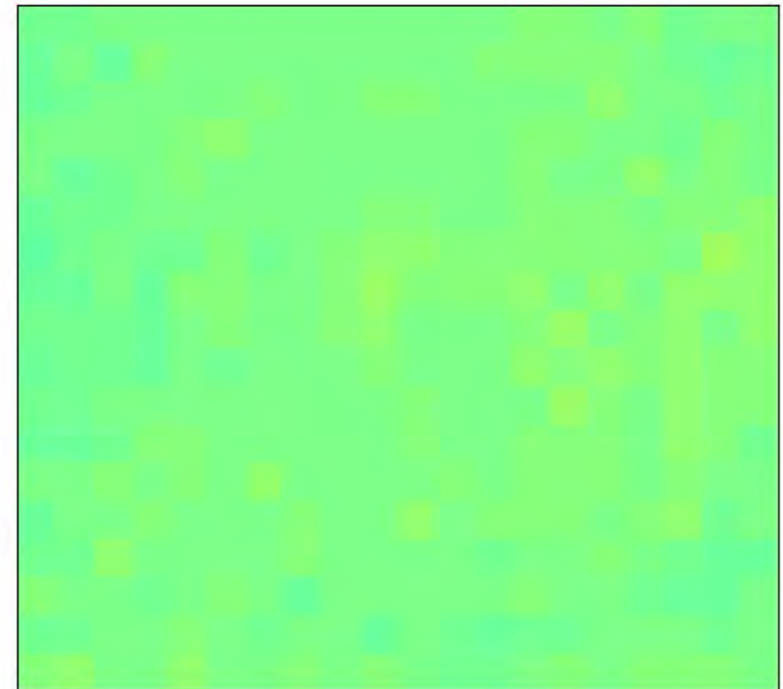
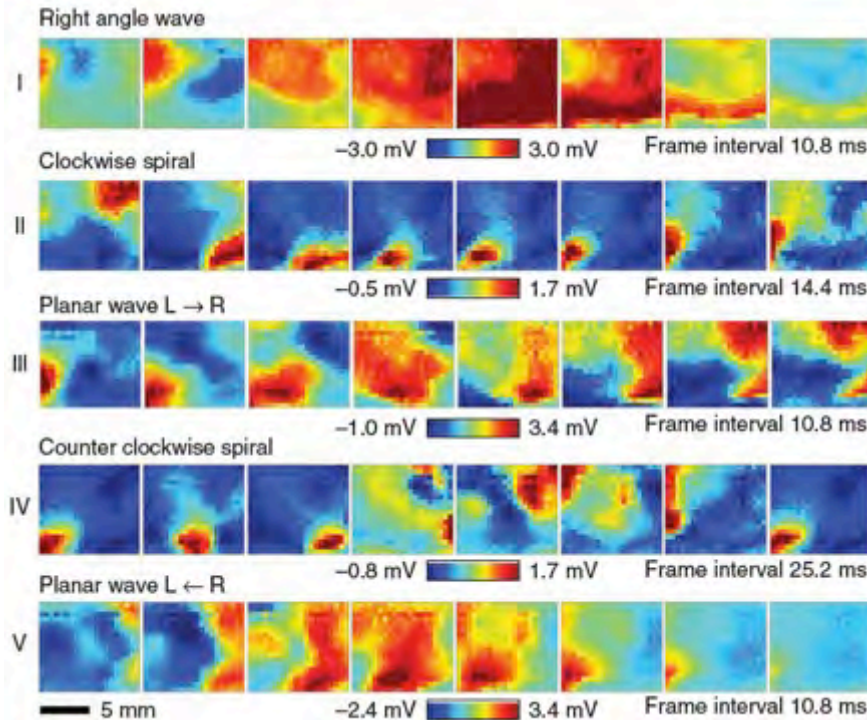
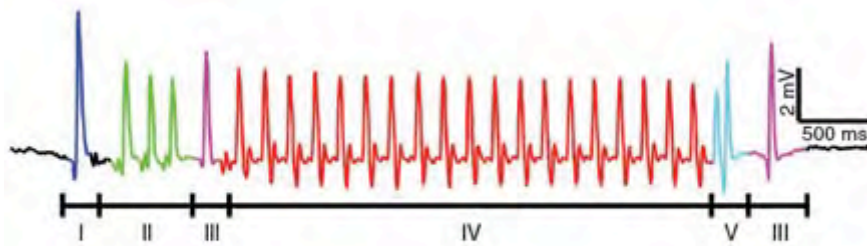


Surface of the brain is not even, and activity in sulci is inaccessible to surface electrodes

Diagnostics through Electrode Arrays

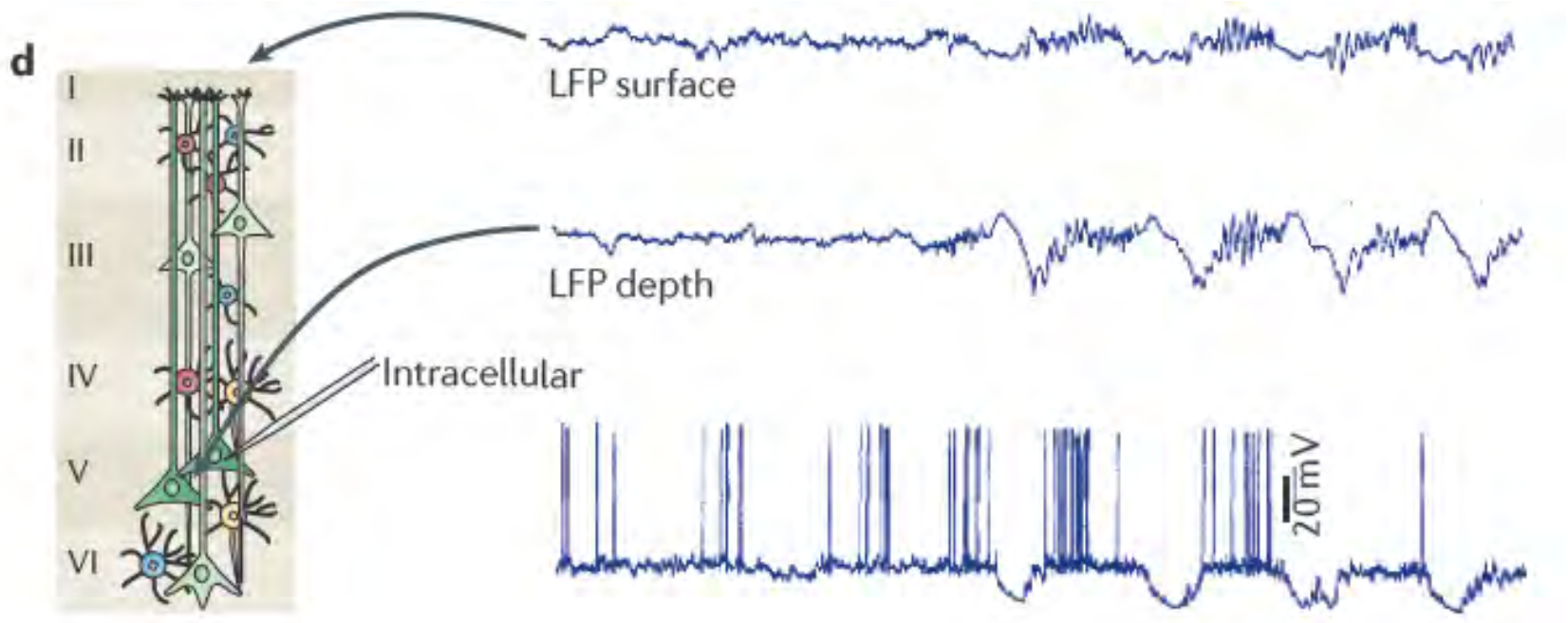
Electrocorticography (ECoG)

Seizures appear as spiral waves of activity on the cortex



Diagnostics through Electrode Arrays

Local Field Potential (LFP)



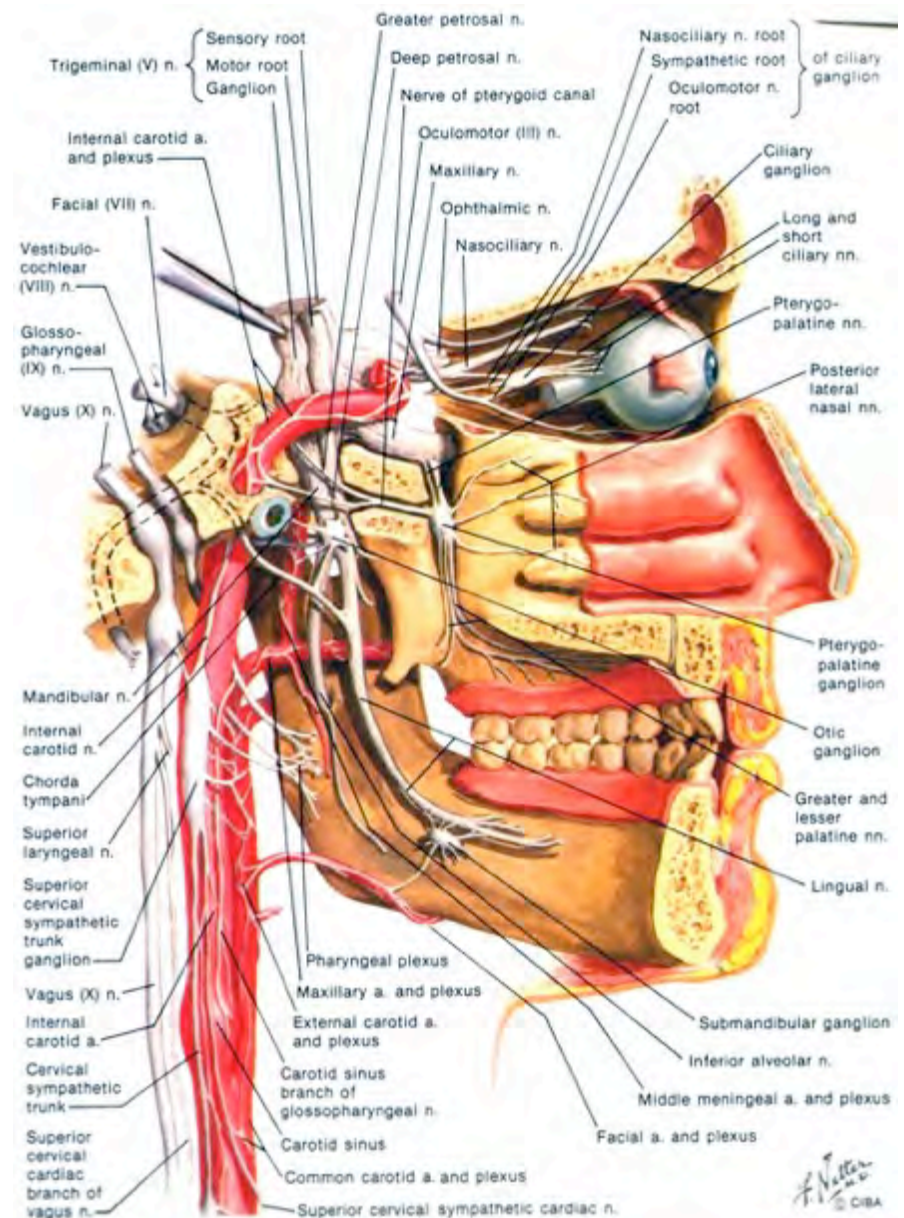
LFP traces from the superficial and deep layers of the motor cortex in an anaesthetized cat and an intracellular trace from a layer 5 pyramidal neuron

Developing treatments for Epilepsy

Stopping Seizures with Electrical Stimulation

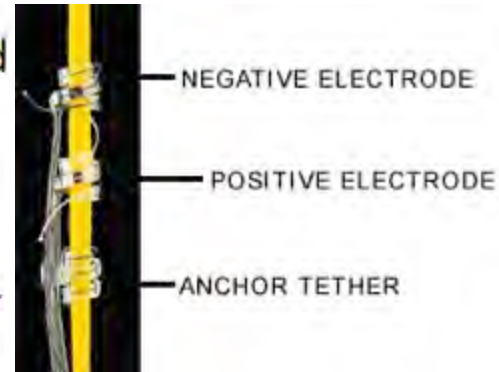
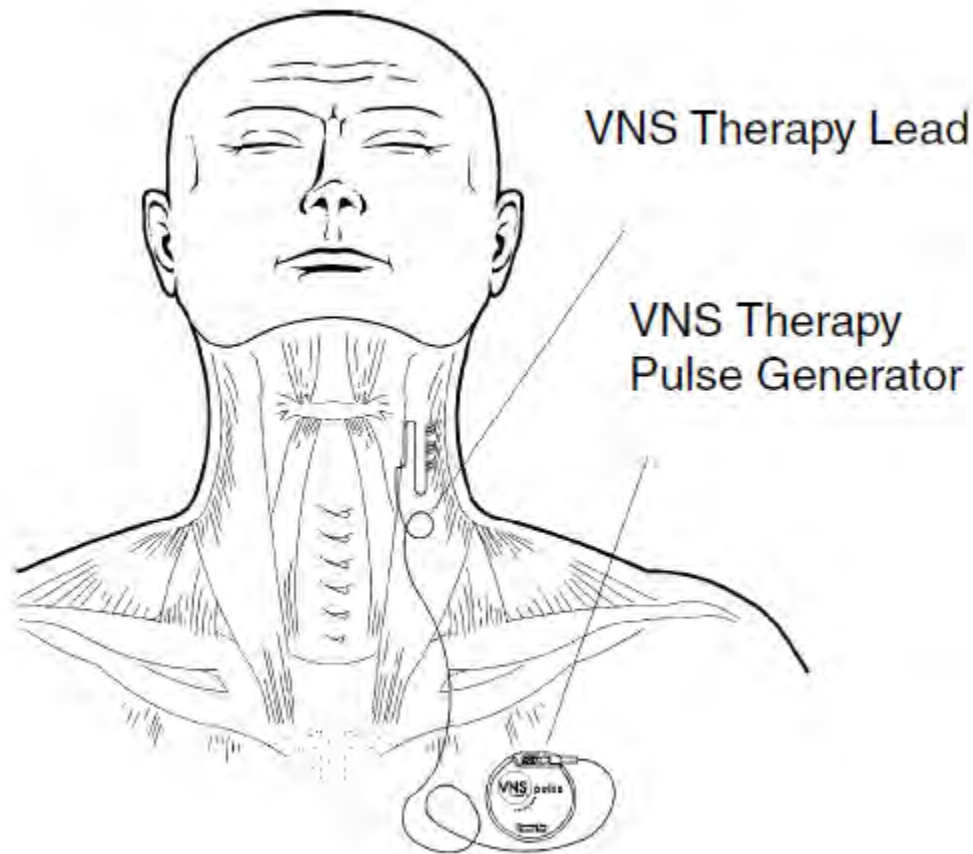
Vagus Nerve Stimulation

- Vagus nerve: innervates heart, larynx, lungs and intestines. Carries sensory information back to the brain.
- Mechanism of action: not understood, but may involve activation of the thalamus and/or release of neurotransmitter norepinephrine interfere epilepsy



Stopping Seizures with Electrical Stimulation

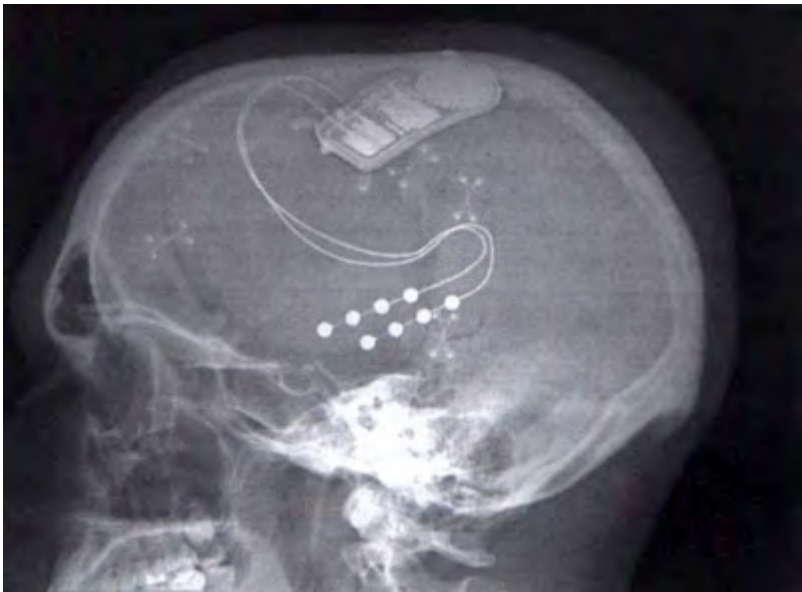
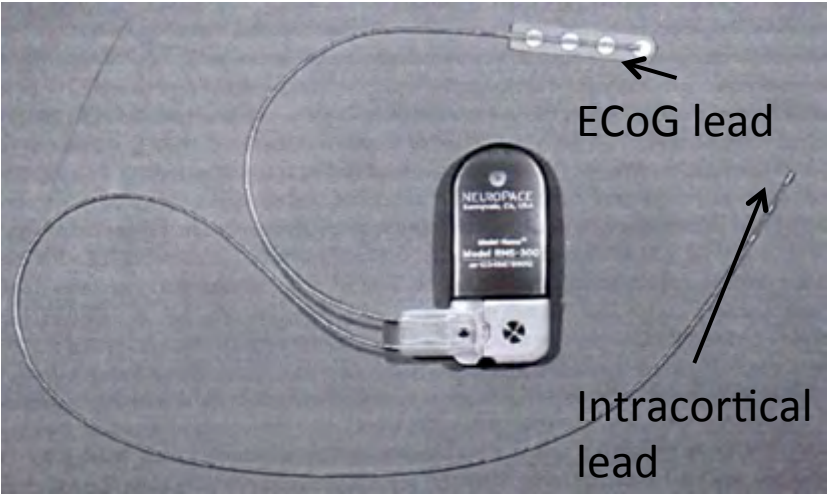
Vagus Nerve Stimulation



Left vagus nerve is used for stimulation because the right vagus nerve affects the heart rate



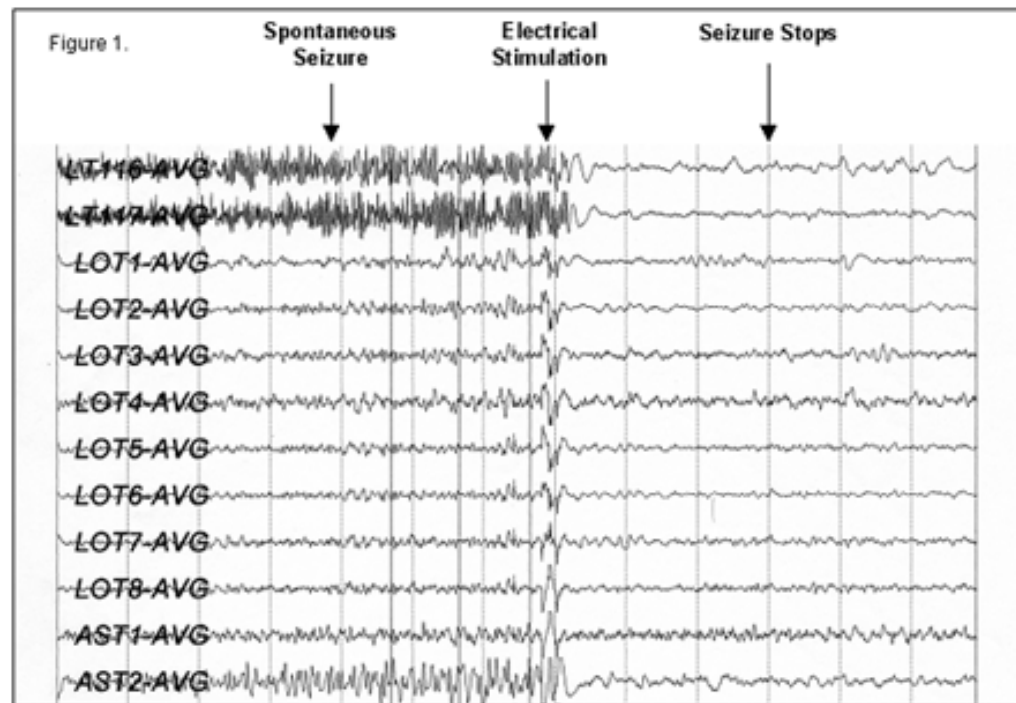
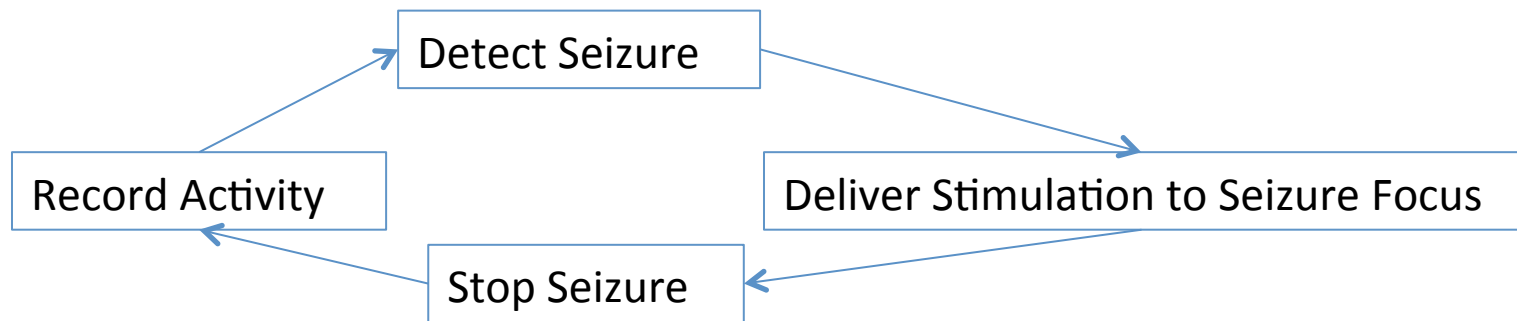
Responsive neurostimulator system



Responsive neurostimulator system (US manufacturer Neuropace)

Stopping Seizures with Electrical Stimulation

Responsive neurostimulator system



Developing treatments for Epilepsy

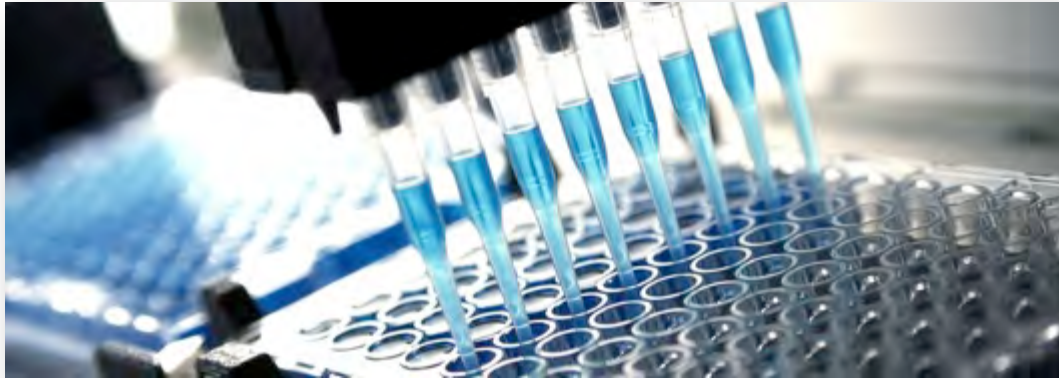
Faster drug development with Brain-on-a-Chip

Drug Discovery Process



Whole process takes more than 10 years, costs over 1 billion dollars

Faster drug development with Brain-on-a-Chip



Cellular assays has been highly successful in new generation of drugs against some types of cancer

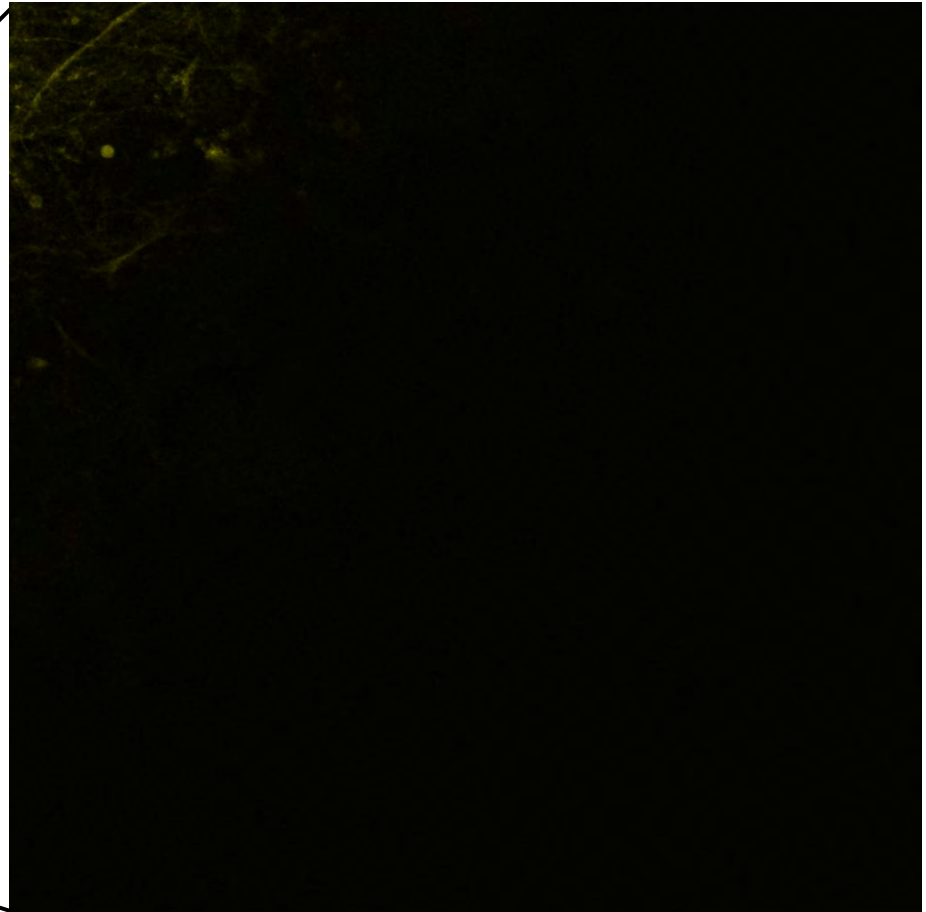
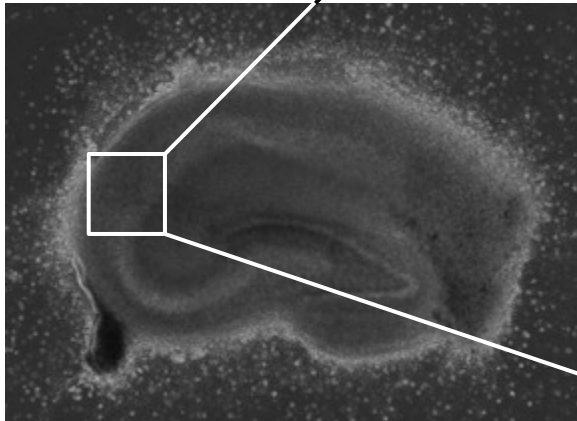
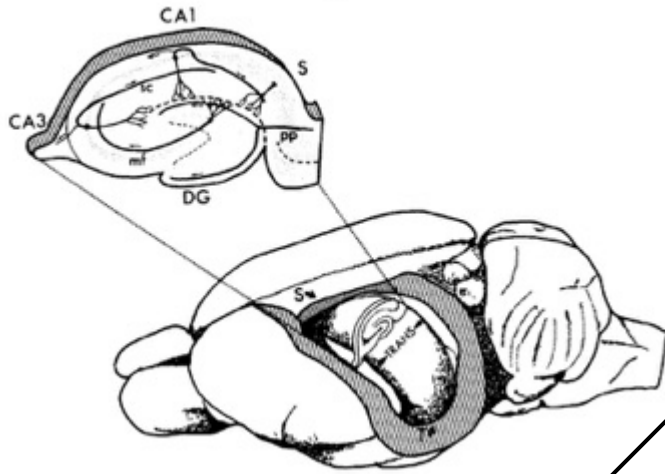
However, there is no simple cellular assay that can be used to assess drug effectiveness in epilepsy which require the presence of a functioning neuronal network

Animal model require time-consuming and expensive surgical procedures for electrode implantation to monitor neuronal activity



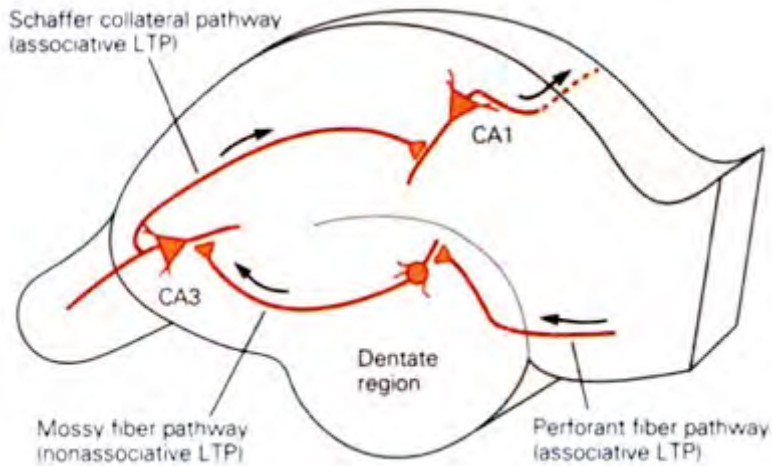
Faster drug development with Brain-on-a-Chip

Organotypic Brain Slice Culture



Faster drug development with Brain-on-a-Chip

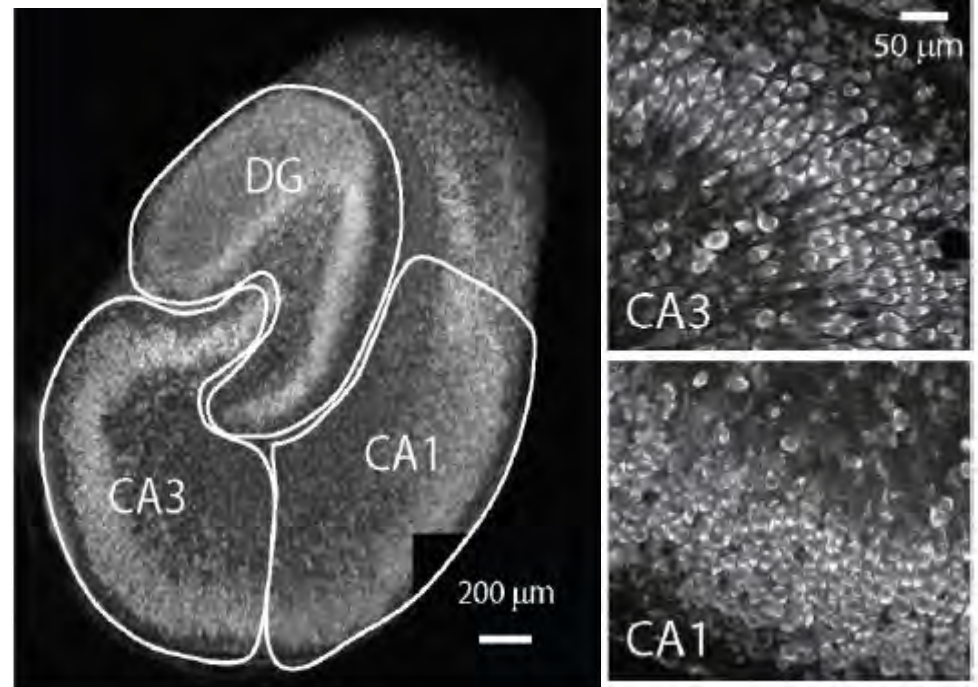
Organotypic Brain Slice Culture



Hippocampal regions CA1, CA3, and dentate gyrus (DG) remain well-preserved and densely packed with neurons

Hippocampus

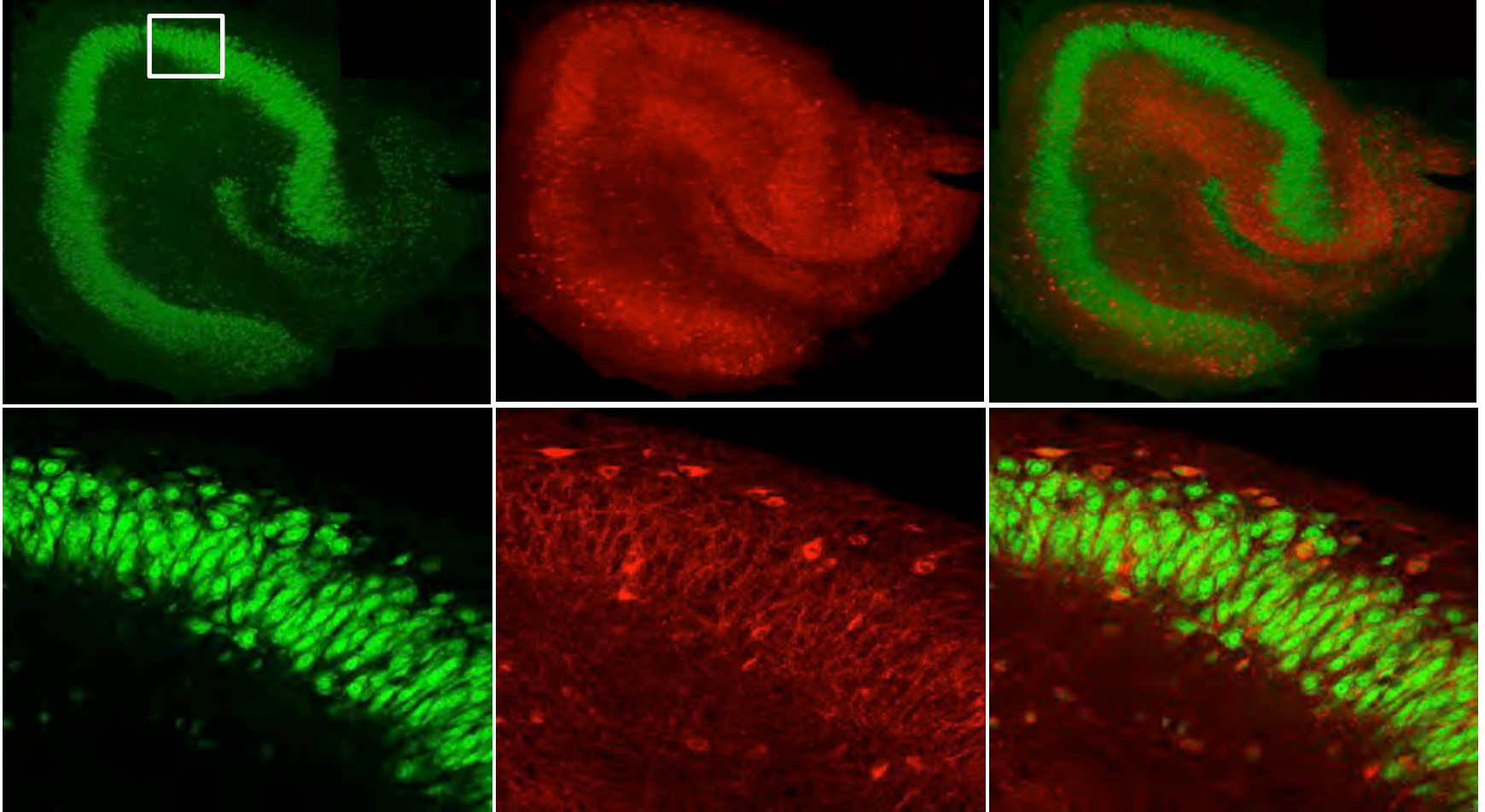
- Neatly organized neural structure
- Crucial in development of epilepsy



Nissl staining of a DIV 28 culture

Faster drug development with Brain-on-a-Chip

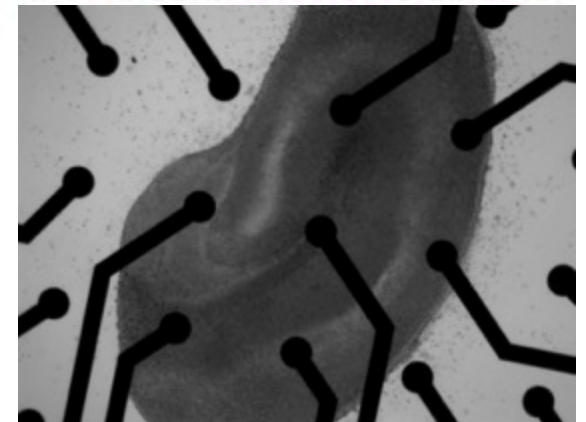
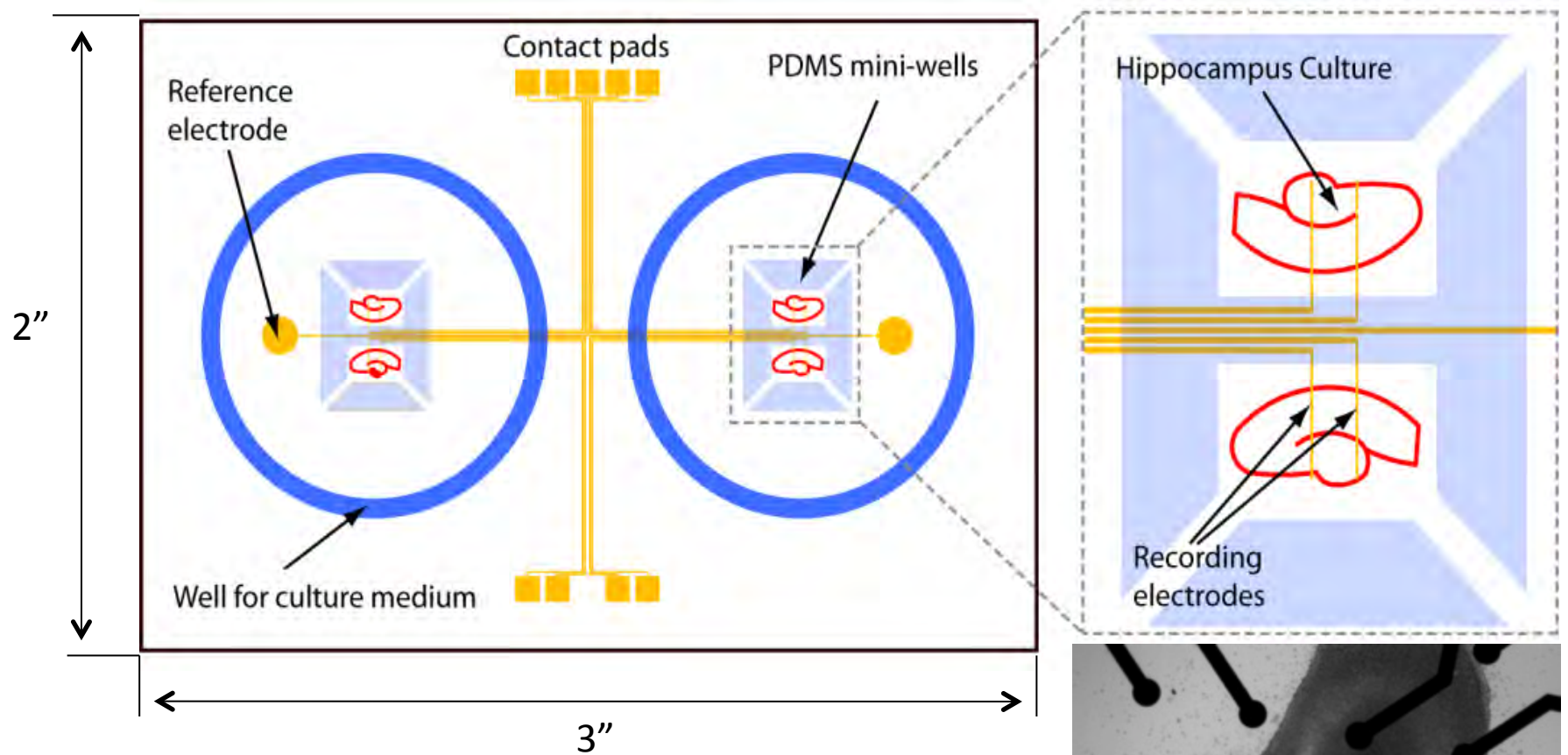
Organotypic Brain Slice Culture



DIV 30 Neural organization of hippocampus. **Excitatory** and **inhibitory** neurons are preserved

Faster drug development with Brain-on-a-Chip

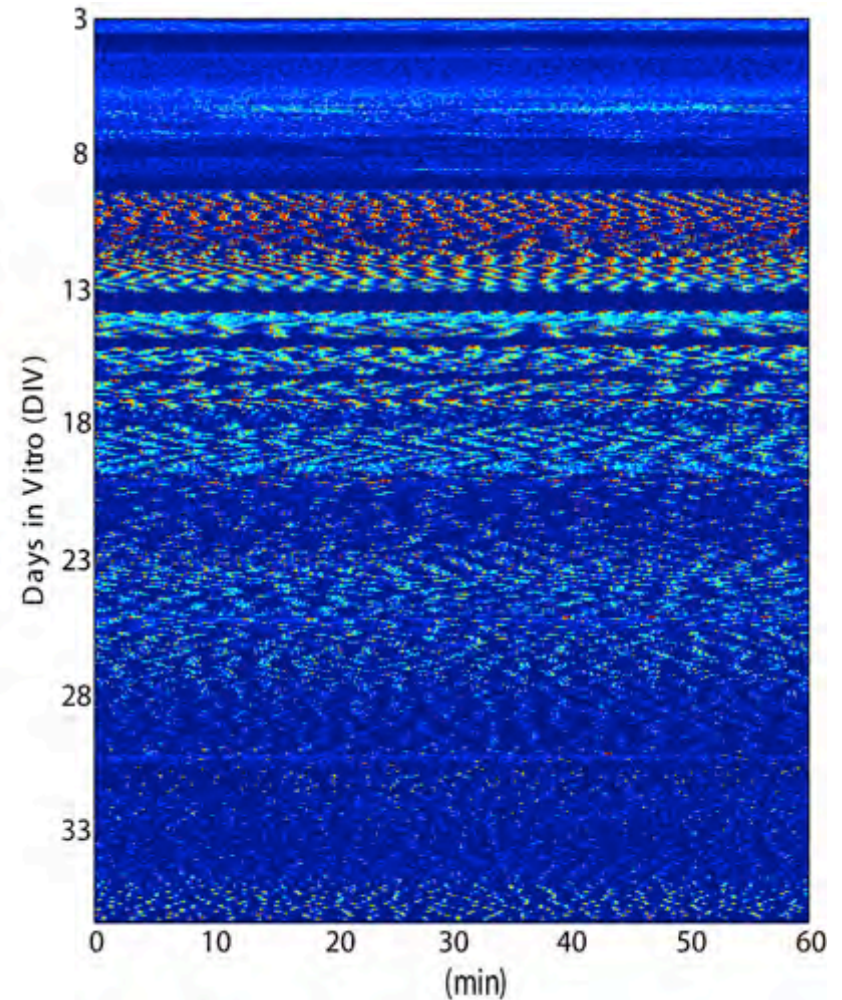
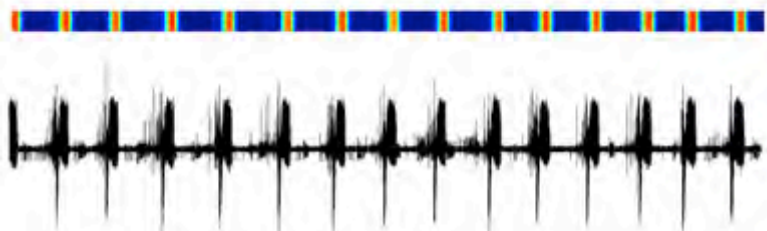
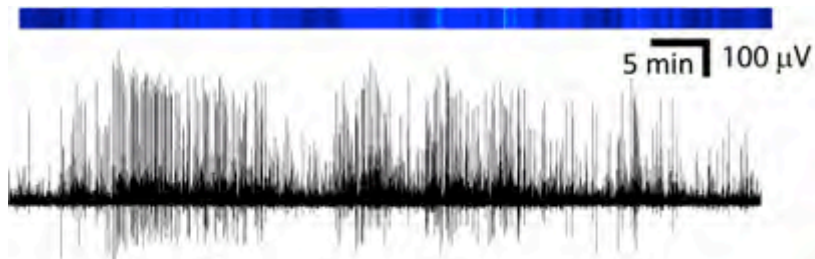
Epilepsy on a Chip



Custom MEA with four organotypic hippocampal cultures

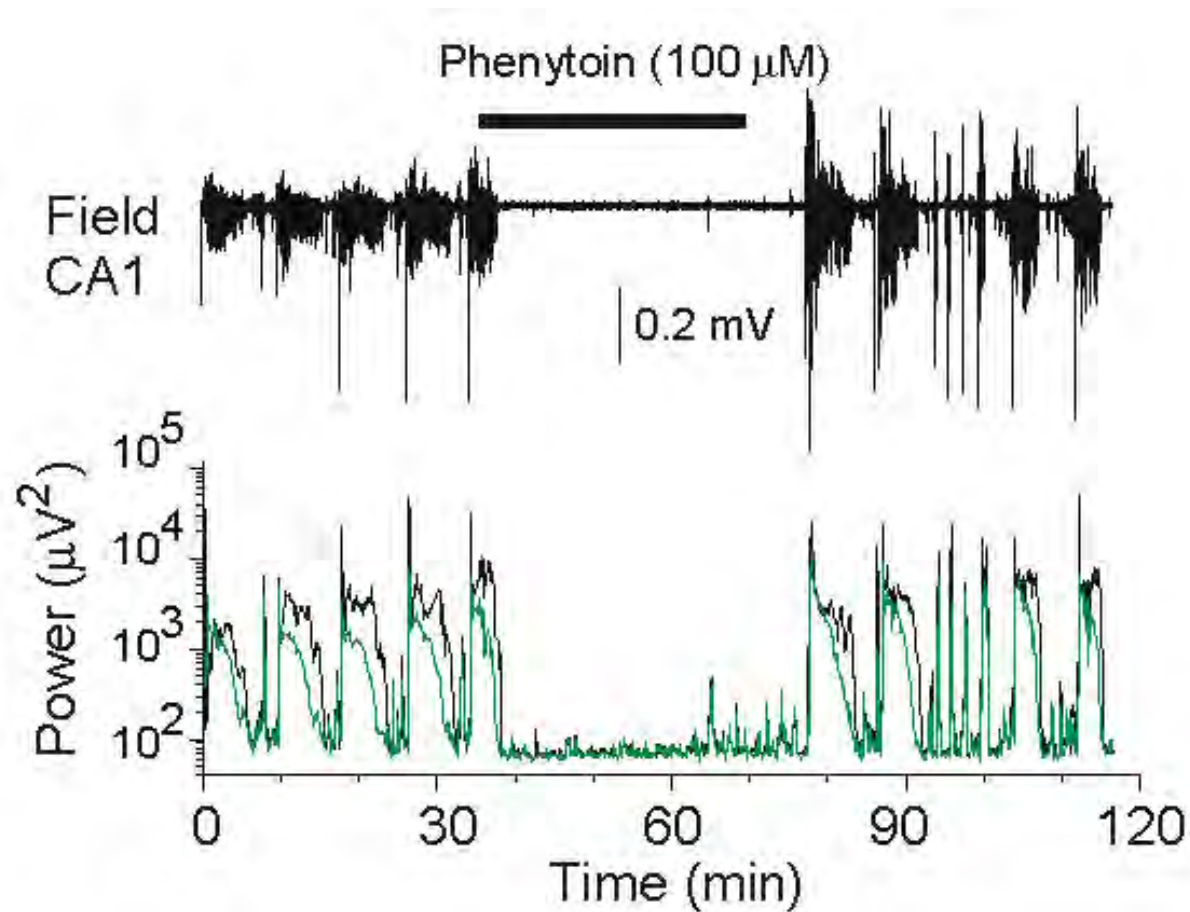
Faster drug development with Brain-on-a-Chip

Epilepsy on a Chip

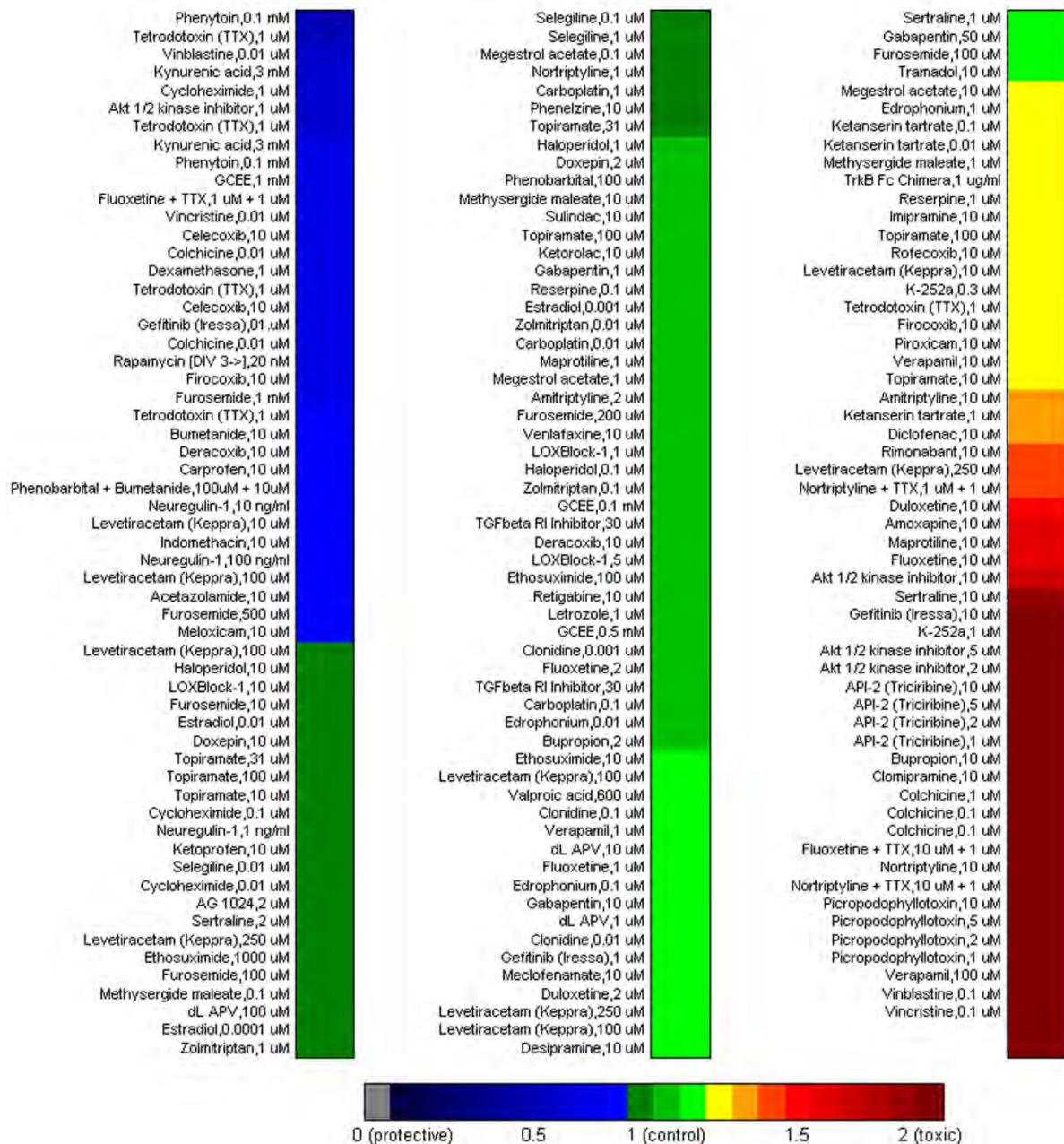


Faster drug development with Brain-on-a-Chip

Epilepsy on a Chip



phenytoin exerted acute, reversible anticonvulsive effects in a model of post-traumatic seizures in vitro, which is the same in epileptic patients



Rapid experiment rate with **epilepsy-on-a-chip** allowed us to evaluate > 150 drugs for antiepileptic effects, with some unexpected candidates emerging

Questions?

Thank you!