

Introduction to the brain

Part III: Brain Research

A brief introduction to experimental
research techniques used to work out
how the brain does what it does

Learning Objectives

To appreciate some of the techniques used in modern neuroscience research

To gain an introduction to the types of data collected in neuroscience research

- this is exactly the type of data we will learn to model later**

To appreciate the difficult nature of these experiments

- and the fact that they yield vast quantities of data that require complicated analysis to be understood**

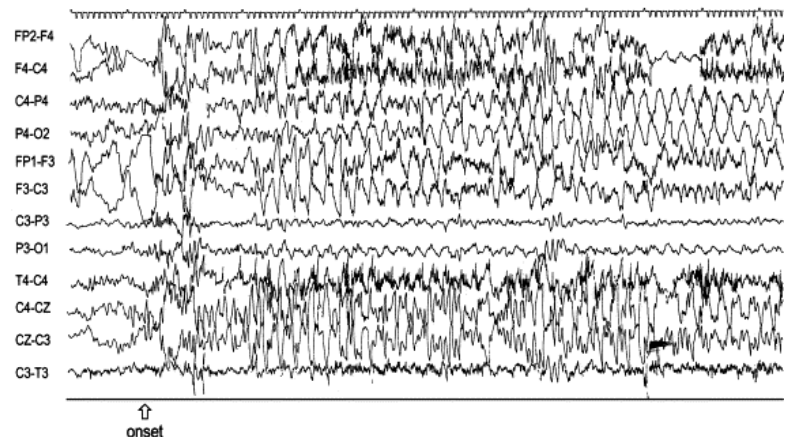
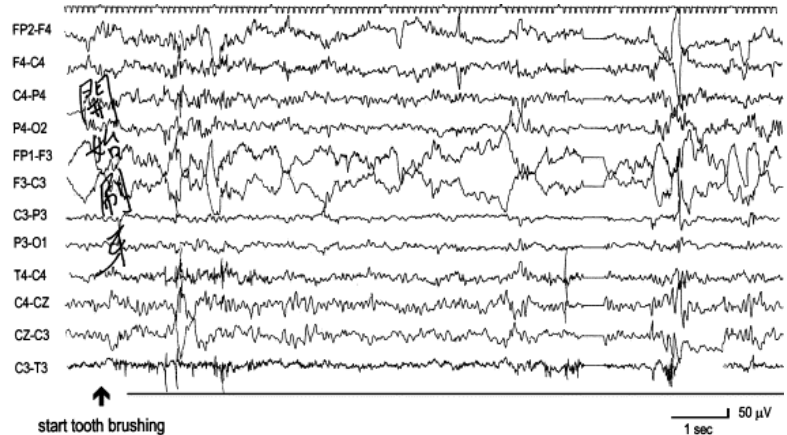
EEG

Electroencephalography (EEG) is a technique used to record voltage changes from the human scalp.

Voltage changes produced from neurons within the brain conduct through the CSF, brain membranes and the scalp and can be recorded from the surface of the head.

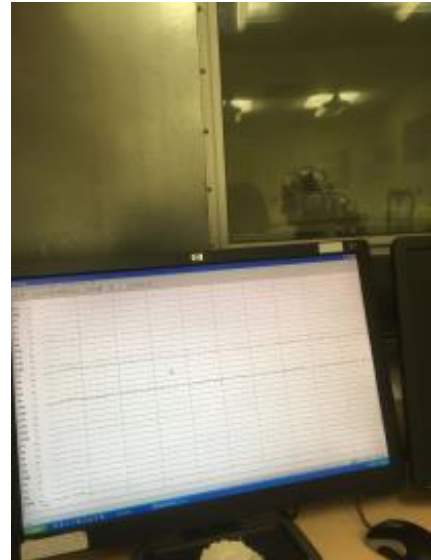
Varying numbers of electrodes: here = 12

Global brain states



Chuang et al. 2004. Tooth-brushing and epilepsy

Electroencephalography (EEG)



ERPs and/or frequency tagging

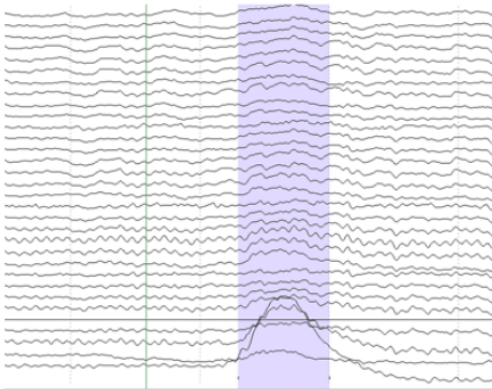
Examples from neurolinguistics

bristol.ac.uk

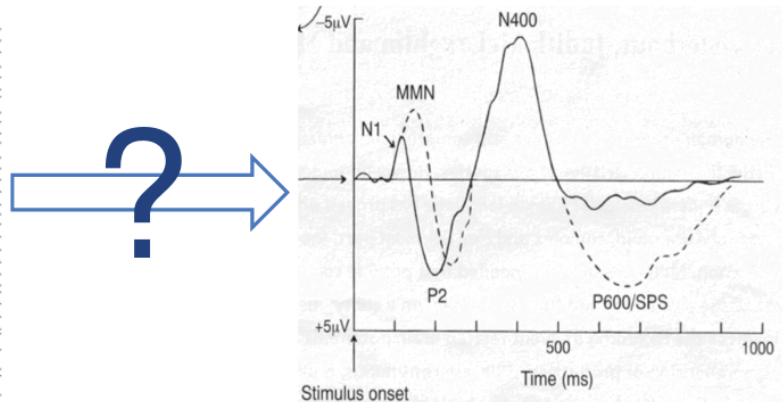
Event-related potentials (ERPs)

Brain response to a single, real word gives a stereotypical ERP (measured in volts)

Raw Data (EEG)



End Products (ERP)



Frequency-tagging EEG

The brain oscillates at different frequencies depending on what the brain is doing.

Brain oscillations can entrain to the rate of stimuli presented during an experiment.

In relation to neurolinguistics, if we present words at a fixed 4Hz rhythm, we can see a corresponding rhythm of 4 Hz in the EEG.

We can take this further and present words at a rate of 4Hz and make each 4 word block represent one sentence, like 'New plans bring hope.', then we have one sentence every second (1Hz). Interestingly we also see a brain response at 1Hz. This allows us to look at how the brain is processing language.

EEG

EEG has a high temporal resolution

- you can see what the brain is doing at a very small time scale

EEG has a very low spatial resolution

- it is hard to isolate the brain region involved in generating the recorded response

Advantages:

- non-invasive: can be used on humans (both adults and children as well as patients)
- relatively inexpensive
- can record the brain in real-time

fMRI



Functional magnetic resonance imaging (fMRI)

fMRI measures the BOLD (blood oxygen level dependent) response

As a brain region becomes active, oxygenated blood is diverted to the active area.

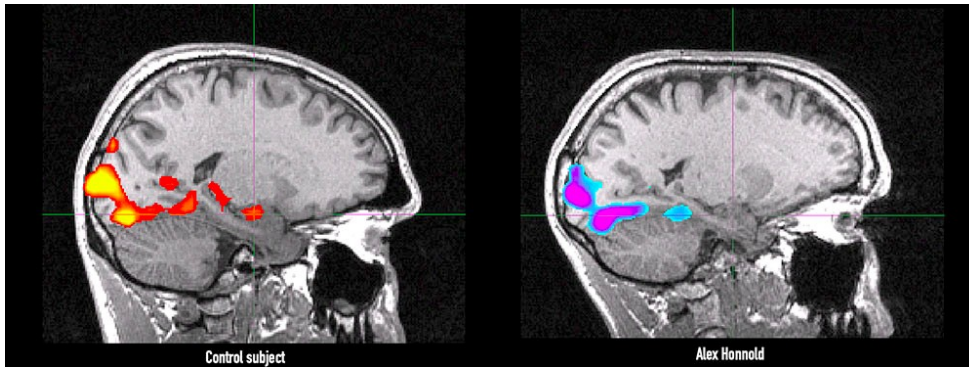
Oxygen in the blood interferes with the magnetic response and gets picked up in the images.

fMRI can therefore be used to help us understand which areas of the brain are involved in processing.

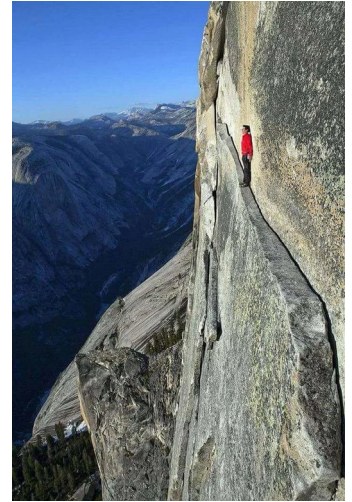
High spatial resolution

Low temporal resolution

Alex Honnold and his amygdala



fMRI imaging shows amygdala activity in a control subject, left, and Honnold, right, when looking at images expected to elicit emotional responses from the viewer. Images courtesy of Dr. Jane Joseph



Useful in computational neuroscience to identify brain regions to include in network models.

Electrophysiology

Like Hodgkin and Huxley, we are able to use recording electrodes to record the activity (changes in voltage or current) from individual neurons and groups of neurons.

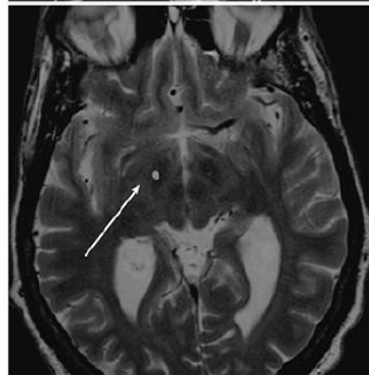
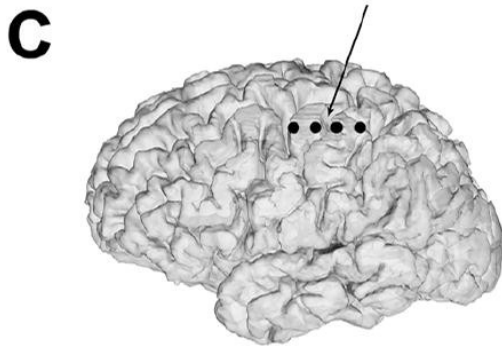
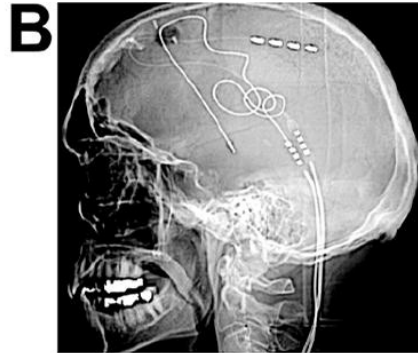
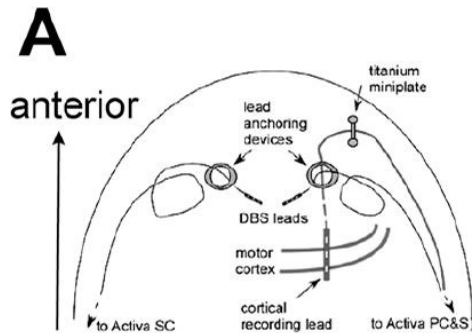
Electrophysiology means to record the activity of neurons.

This can be done *in vivo* (whole animal) or *in vitro* (in a dish, often a brain slice).

Recordings can be made from inside the cell (intracellular) or outside the cell (extracellular)

Neurons can occasionally be recorded from the human brain, but it is much more common to use rodents, or cells grown in a dish.

In vivo Electrophysiology in humans



In severe cases of epilepsy or Parkinson's disease, electrodes can be implanted into the brain to help alleviate symptoms. These can also record brain activity.

Jennifer Anniston cell

Ventro-tegmental area (VTA)

Chronic multisite brain recordings from a totally implantable bidirectional neural interface: experience in 5 patients with Parkinson's disease, Journal of Neurosurgery, Swann et al., 2018

In vivo electrophysiology in rodents

More commonly rodents are used in these studies.

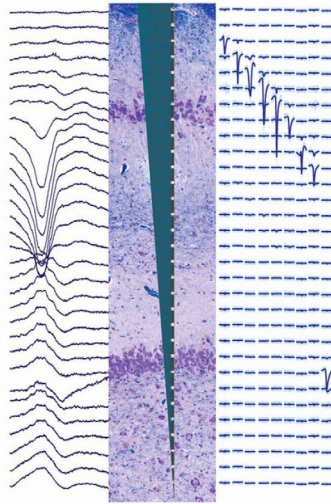
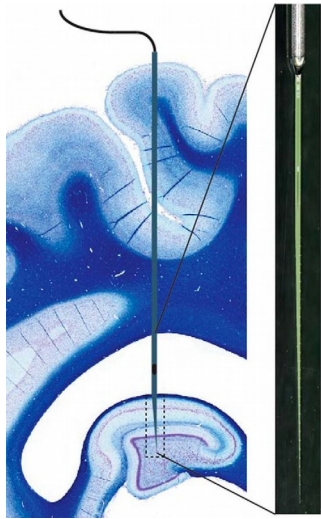
We now have extremely good technologies and we can put in probes with hundreds of different sites to record hundreds of neurons simultaneously in different areas.

Recordings are made from outside the cell = extracellular

Advantages:

- record in real time
- animal is awake: this means we can record during behaviour, eg. learning
- can isolate single cells or look at more global activity (LFPs = local field potentials)
- can apply drugs or stimulation at the same time

In vivo electrophysiology in rodents



Electrophysiological Signature Reveals Laminar Structure of the Porcine Hippocampus, Ulyanova et al.

From: <http://neuroscience.cornell.edu/faculty.html>

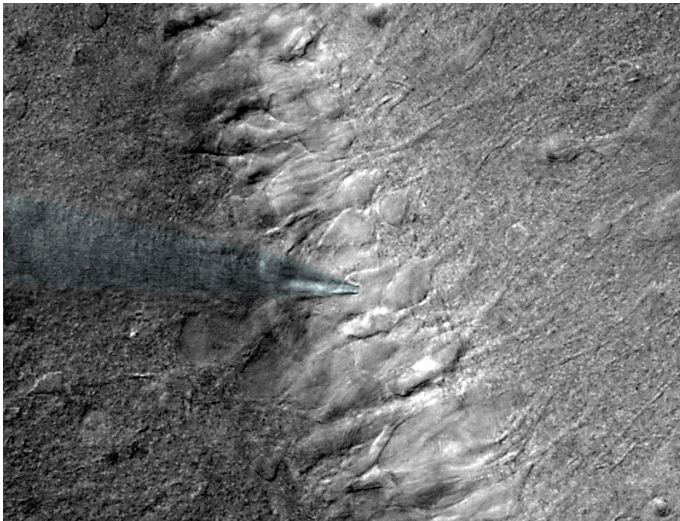
A place cell spiking

<https://www.youtube.com/watch?v=vOJKID4ukbY>

In vitro electrophysiology – patch clamping

Neuroscientists are also able to record from inside cells = intracellular.

This can be done in whole animals but more typically brain slices are used.



During intracellular patch clamping, an electrode is used to pierce the cell and record from the inside.

You can record voltage, or current!

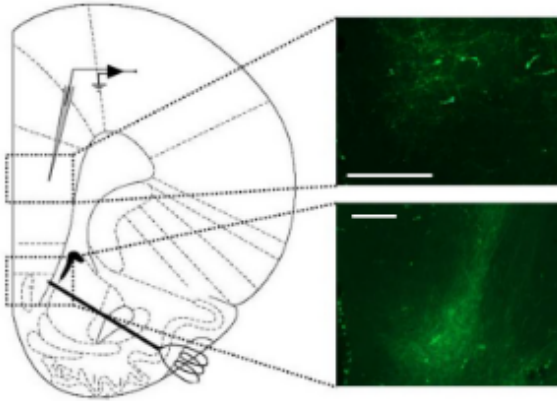
In vitro electrophysiology – patch clamping

Being inside the cell is interesting because you can record subthreshold activity.

That means you can record not just the action potentials, but also the decreases in membrane potential brought about by an inhibitory cell, or excitatory inputs that are not strong enough to elicit an action potential.

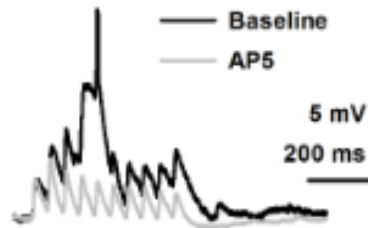
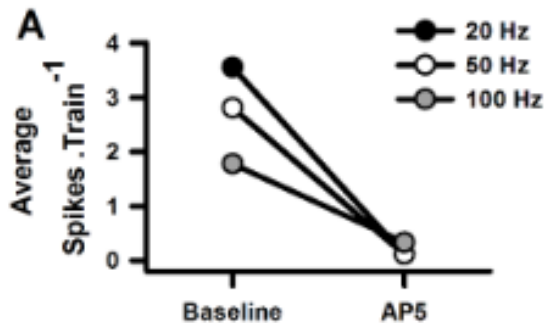
You also have more control over the environment and are able to apply certain chemicals to block specific channels and look at the effect on the cell activity. Or you can apply drugs.

Example patch clamping data



This is from a study looking at how NMDARs affect transmission from HPC-PFC.

Block NMDARs with AP5 = block summation of subthreshold activity and stop spiking.



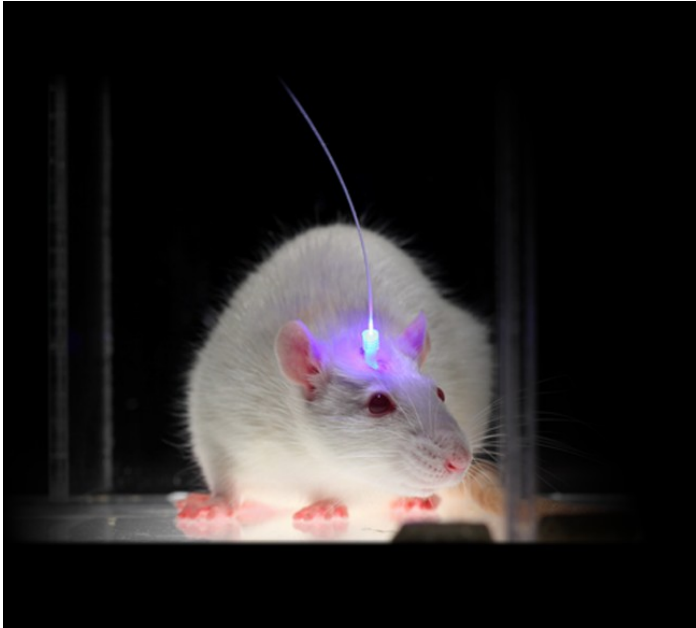
Calcium imaging – Zebra fish

Calcium imaging takes advantage of the fact that when an action potential arrives at the axon terminal, it causes a huge rise in intracellular calcium concentration.

Calcium imaging uses calcium indicators that fluoresce when they bind to calcium. This fluorescence can be measured using a microscope.

There is a delay and the temporal resolution is not as acute as with recording electrodes but it is less invasive and you can measure huge quantities of neurons.

Optogenetics



Optogenetics is a technique whereby you modify the genes within a cell (typically using a virus) so that they express channels that can be controlled using light. This means you can control when a neuron is active or inactive.

Conclusions

Experimental neuroscience involves research on humans and animals

Using electrodes we can record the electrical changes that occur in and around neurons spontaneously or following stimulation

Electrophysiology = recording electricity (voltage or currents)

In vivo electrophysiology = whole organisms

In vitro electrophysiology = brain slices or cells in a dish

Optogenetics allows you to manipulate the behaviour of specific target neurons using light, you can combine this with electrophysiology to record to consequences of these manipulations on other neurons

Calcium imaging allows you to visualise, using a microscope, the activity of hundreds (if not thousands) of cells at the same time