University of BRISTOL

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

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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

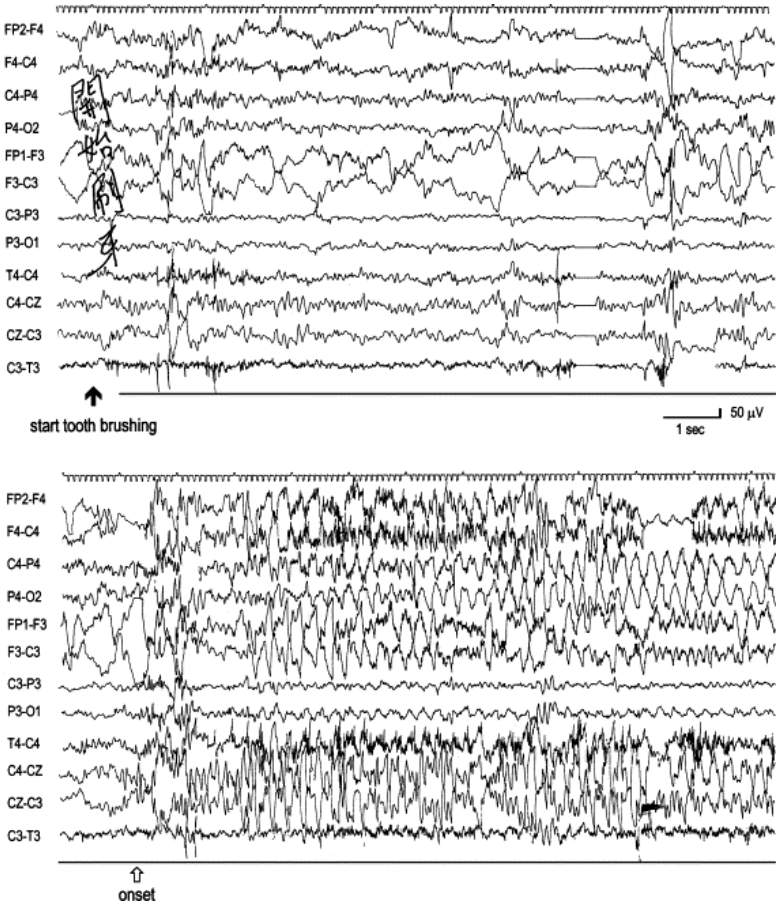
EEG

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.

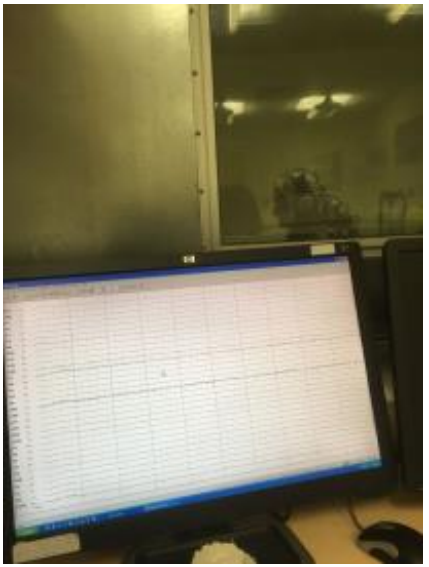
Varying numbers of electrodes: here = 12

Global brain states



Chuang et al. 2004. Tooth-brushing and epilepsy

Electroencephalography (EEG)



ERPs and/or frequency tagging

Examples from neurolinguistics

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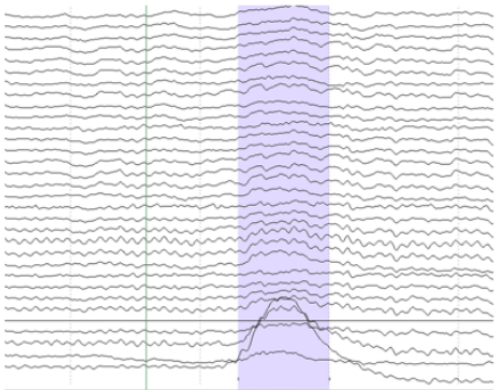
Event-related potentials (ERPs)

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

Raw Data (EEG)



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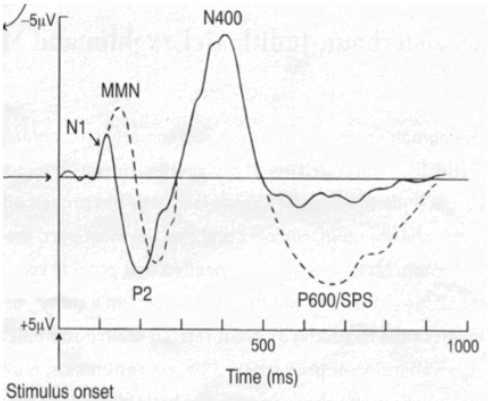
End Products (ERP)



Frequency-tagging EEG

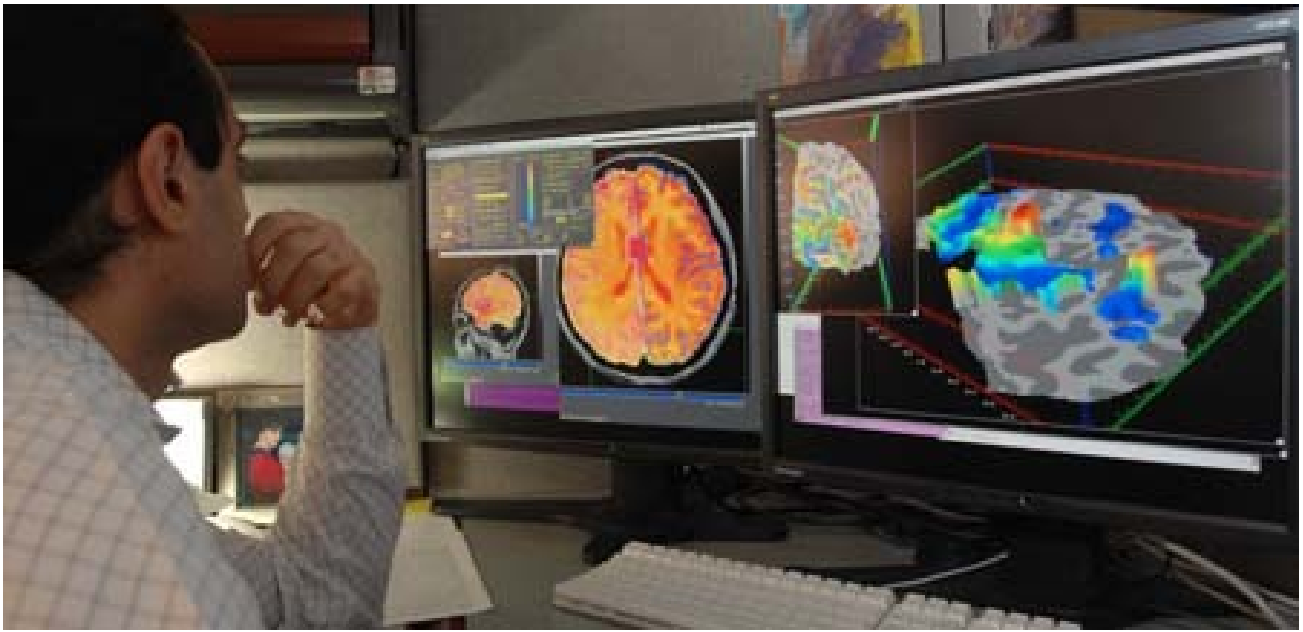
The brain oscillates at different frequencies depending on what the brain is doing.

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.

FMRI



From wikipedi

Functional magnetic resonance imaging (fMRI)

fMRI measures the BOLD (blood oxygen lovel dependent) response

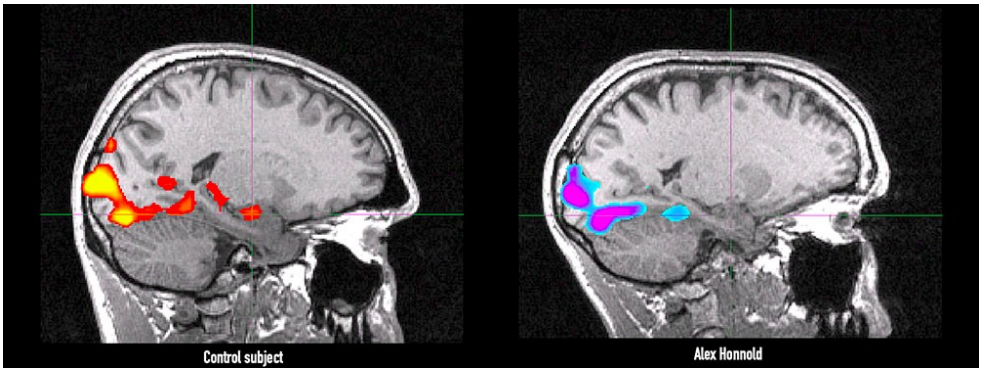
As a brain region becomes active, oxygenated blood is diverted to the active area.

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

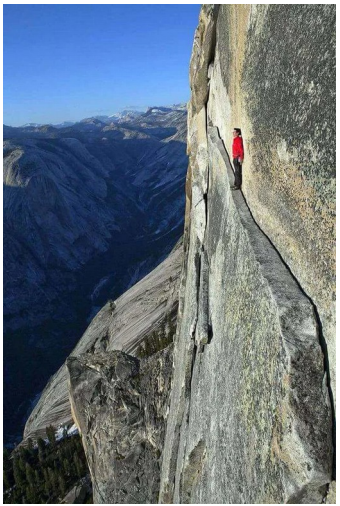
fMRI can therefore be used to help us understand which areas of the brain are involved in processing.

From wikipedi

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

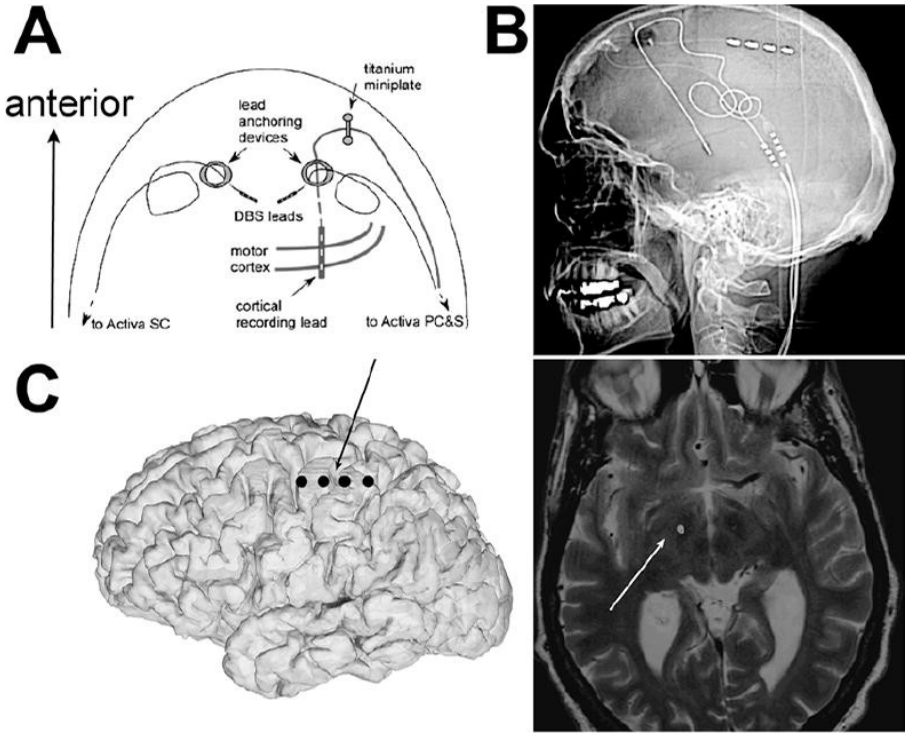
Like Hodgkin and Huxley, we are able to use recording electrodes to record voltage from individual neurons and groups of neurons.

In order to do this electrodes must be implanted into the brain.

Typically these are extracellular recordings and record the voltages from outside the cell.

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 people get electrodes implanted into their brain to help alleviate symptoms. These can also record brain activity.

Jennifer Anniston cell

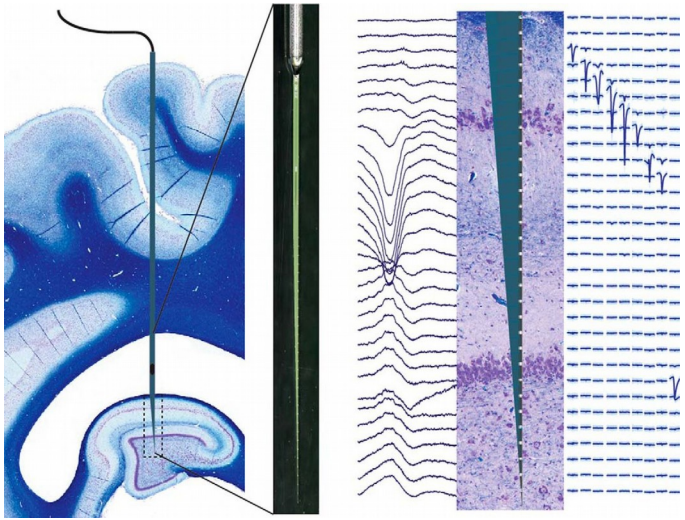
Ventro-tegmental area (VTA)

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.



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

From: http://neuroscience.cornell.edu/facult

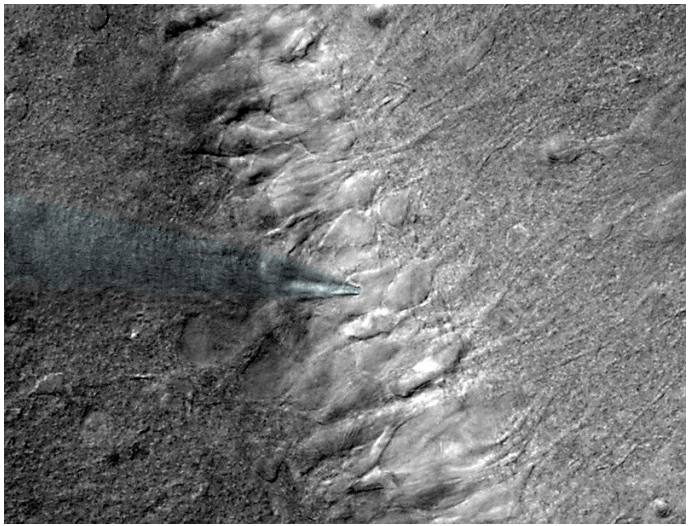
A place cell spiking

https://www.youtube.com/watch?v=vOJKlD4ukbY

In vitro electrophysiology – patch clamping

Neuroscientists are also able to record the voltage 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!

From: https://en.wikipedia.org/wiki/Patch_clamp

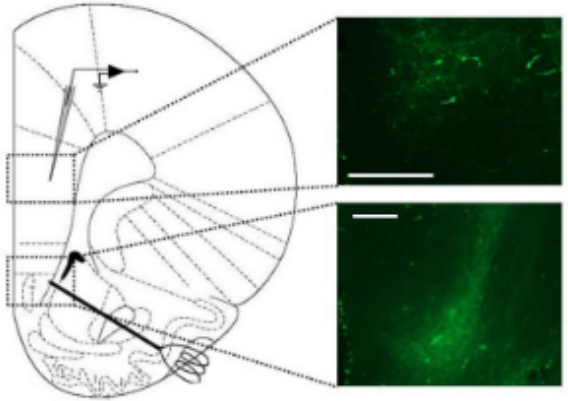
In vitro electrophysiology – patch clamping

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 bought about by an inhibitory cell, or excitatory inputs that are not strong enough to elicit an action potential.

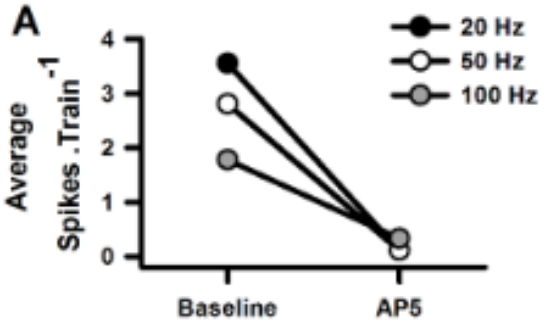
You also have more control over the environment and are able to apply certain chemicals to block specific channels and look at the effect on the cell activity. Or you can apply drugs.

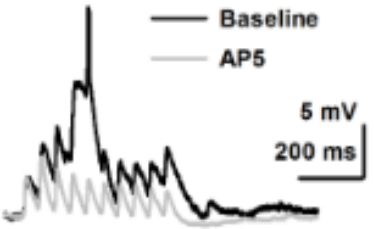
Example patch clamping data



This is from a study I did at UoB back in 2012 looking at how NMDARs affect transmission from HPC-PFC.

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





P. Banks, A. Burroughs et al., 2015: NMDARs control hippocampal-PFC synaptic transmission

Calcium imaging – Zebra fish

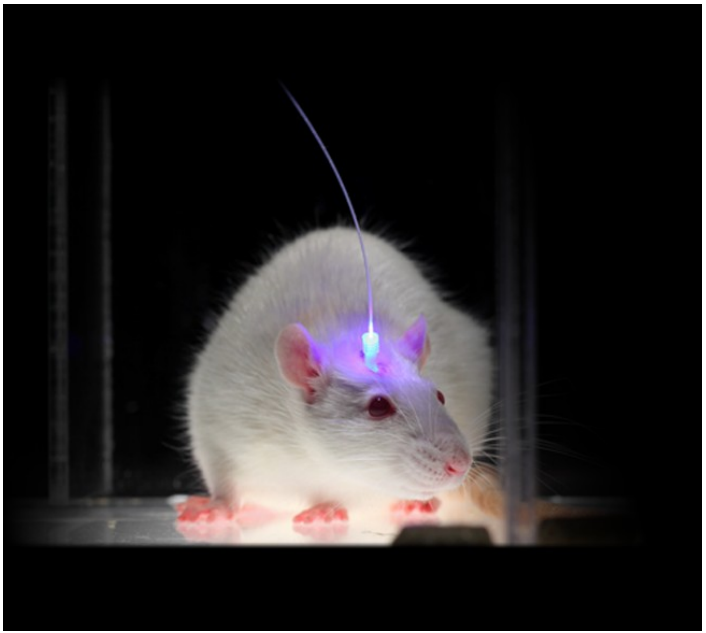
Calcium imaging takes advantage of the fact that when an action potential arrives at the axon terminal, it causes a huge rise in intracellular calcium concentration.

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.

https://www.youtube.com/watch?v=q40dtdkZUN4

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.

From: http://web.stanford.edu/group/dlab/optogenetics/

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