Introduction to Computational Neuroscience

Lecture 3: Windows to the brain
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**Basics**

**Analyses**

**Models**

**Cognitive**

**Applications**
“One of the difficulties in understanding the brain is that it is like nothing so much as a lump of porridge”

R.L. Gregory
Every leap forward in knowledge about the NS has been based on a leap forward in technology.
Some leaps forward

Ramon y Cajal (1900s) → Golgi staining → Structure of the NS

Eccles, Hodgkin, Huxley (1940s) → Intracellular recordings → Ionic basis of membrane potential

Hubel, Wiesel (1960s) → Extracellular recordings → Information processing in visual system

Neher, Sakmann (1970s) → Patch-clamp → Physiology of single-ion channels
Learning objectives

- Explain the different ways of studying the NS
- Compare strengths and limitations of different techniques to measure brain structure and activity
- Understand the basic mechanisms behind different brain imaging techniques and electrophysiology
Levels of study

A neuroscientist can study the NS through any level of organization.

Different techniques are appropriate for different scales.

However, irrespective of the technique the basic scientific approach is consistent from level to level.
Methods of studying the NS

1) Examining case studies
2) Screens
3) Descriptions
4) Manipulations
Methods of studying the NS

1) **Case study**: is an example of an event that happened to a subject (human or group of humans) that demonstrates an important role for an aspect of the NS.

* Non-repeatable
* Not a true experiment (but very informative)
Methods of studying the NS

2) **Screen**: is a search for anatomical structures, neurons, proteins or genes that may play a role in a biological process of interest.

* Often explorative rather than driven by hypothesis
* Identifies candidates for future hypothesis-driven research
3) **Description:** is the act of simply observing properties of the NS without manipulation.

* Foundation for understanding structure-function
* Provides insight about what variables manipulate

Ex.: quantifying the number or types of neurons belonging to one region, the magnitude of a neuronal response to certain stimulations, etc...
Methods of studying the NS

4) Manipulation: consists of varying one aspect of the NS or environment and examining the effect this perturbation has on a separate aspect of the NS

* Tests the effect of $X$ (independent variable) on $Y$ (dependent variable)

**Loss-of-function** (necessity) experiments

Is the activity in region $X$ necessary for behavior $Y$?

**Gain-of-function** (sufficiency) experiments

Can stimulation of region $X$ cause behavior $Y$?
Techniques for imaging and recording the brain
Whole brain imaging

Electrophysiology

Neuronal manipulation
Neuroimaging

**Structural brain imaging** techniques are used to resolve the anatomy of the brain in a living subject without physically penetrating the skull.

- Measure anatomical changes over time
- Diagnose diseases such as tumors or vascular disorders

**Functional brain imaging** techniques are used to measure neural activity without physically penetrating the skull.

- Which neural structures are active during certain mental operations?
Structural brain imaging

**Neural cell bodies:** biomolecules + proteins + carbohydrates

**Axons:** fat (myelin)

**Ventricles:** cerebro-spinal fluid (saline solution)

The goal: to use these differences in composition to form the basis of an image.
Structural brain imaging

**Contrast:** absorption of X-rays

Standard X-ray technology alone cannot produce detailed images of the brain (poor soft-tissue contrast)
Structural brain imaging

Solution 1: insert a dye that absorbs X-ray better than surrounding tissue
Solution 2: take multiple scans from multiple angles and combine them.

**Figure 1.3**

**Figure 1.4**
Computerized tomography (CT). (A) During an imaging session, a narrow beam of X-rays is slowly rotated around a subject's head to hit a detector on the opposite side. Signals from around the head are combined into a computer program that constructs a composite picture based on the various X-ray angles. (B) A modern CT scan can distinguish between gray and white matter, differentiate ventricles, and depict structures with a spatial resolution of millimeters. (B: Reprinted from Nolte, J. and Angevine, J. B., (2007). *The Human Brain in Photographs and Diagrams*, 3rd ed. with permission from Mosby/Elsevier: Philadelphia.Courtesy of Dr. Raymond F. Carmody.)
Structural brain imaging

**Neural cell bodies:** biomolecules + proteins + carbohydrates

**Axons:** fat (myelin)

**Ventricles:** cerebro-spinal fluid (saline solution)

**The goal:** to use these differences in composition to form the basis of an image
Magnetic Resonance Imaging

Contrast: magnetic properties

The Method of imaging the brain in clinics and research

Resolution < 1mm
Magnetic Resonance Imaging

MRI takes advantage of the differential magnetic properties of neural tissue to produce an image.

Utilizes magnetic properties of $H^+$ (abundant)

Artificially excite $H^+$ and measure their relaxation.
Subject is placed in a magnetic field to affect the hydrogen protons in subject’s tissues.
Protons can be thought as miniature magnets that align in the presence of a strong magnetic field.
MRI: physical basis (3)

Protons precess with a frequency that depends on the external magnetic field (generated by the MRI scanner; 1.5-3 Teslas)

A RF pulse at the same precession frequency perturbs the protons. The times of relaxation in the longitudinal (T1) and transversal (T2) axes are measured.
MRI: generating the image

Different substances have different T1 and T2 time constants
RF pulse only excite protons with the same precession frequency

Apply an external magnetic field at a gradient, the RF affects only an specific plane

Voxel: 3d version of pixel represents cubic volume of brain space
MRI: + and -

**Advantages**

Beautiful images with great resolution

Entirely non-invasive

No X-rays applied

**Disadvantages**

Expensive

CT better at bony structures

Not for everybody (e.g. pacemakers)
MRI: tracing connections

MRI can be tweaked to track fiber tracts (bundles of axons)

Diffusion tensor imaging: takes advantages that diffusion of water molecules is faster along fibers

Which areas of the brain are connected

No direction of the connections
Neuroimaging

Structural brain imaging techniques are used to resolve the anatomy of the brain in a living subject without physically penetrating the skull.

- Measure anatomical changes over time
- Diagnose diseases such as tumors or vascular disorders

Functional brain imaging techniques are used to measure neural activity without physically penetrating the skull.

- Which neural structures are active during certain mental operations?
Functional brain imaging

The brain is **bloody** and **electric**

**Blood**
Increase in neuronal activity → increase in metabolic demand for glucose and oxygen → increase in cerebral blood flow to the active region

**Electricity**
Neurons communicate by producing tiny electrical impulses

Blood flow is an indirect, slow measure of neural activity

Electricity is a direct measure of neural activity
Functional brain imaging

- **Positron emission tomography (PET)**
  - Excellent spatial resolution (~1-2mm)
  - Poor temporal resolution (~1sec)

- **Functional magnetic resonance imaging (fMRI)**
  - Hemodynamic techniques

- **Electroencephalography (EEG)**
  - Electro-magnetic techniques
  - Poor spatial resolution (esp. EEG)
  - Excellent temporal resolution (<1msec)

- **Magnetoencephalography (MEG)**
  - Excellent spatial resolution (~1-2mm)
  - Poor temporal resolution (~1sec)
First functional brain imaging
Functional MRI (fMRI)

**Contrast:**
magnetic properties (Blood Oxygenation Level Dependent (BOLD) signal)

Blood is more oxygenated in an activated region of the brain than in a nonactivated region.

Oxyhemoglobin and deoxyhemoglobin differ in their magnetic susceptibility: Deoxy Hb has a higher magnetization decay rate than Oxy Hb.
Functional MRI (fMRI)

Subtraction method

Hand Clenching

Rest

Subtraction

Statistical Parameter Map

Overlay onto Anatomical Image

Supplementary Motor Area

Primary Motor
Functional MRI (fMRI)

Cortical Activity during Hand Movement

Contralateral Hemisphere

Ipsilateral Hemisphere

Healthy Subjects (Right Hand)

Stroke Patients Affected Hand (Right Hand)
fMRI: + and -

**Advantages**
- Good spatial resolution (1-5 mm)
- Entirely non-invasive
- Rich data analysis

**Disadvantages**
- Temporal resolution (seconds due to the hemodynamic lag)
- Expensive
- Geography not mechanisms
Functional brain imaging

Non-invasive recording from human brain (Functional brain imaging)

Hemodynamic techniques

Positron emission tomography (PET)

Excellent spatial resolution (~1-2mm)
Poor temporal resolution (~1sec)

Functional magnetic resonance imaging (fMRI)

Electro-encephalography (EEG)

Excellent temporal resolution (<1msec)

Magneto-encephalography (MEG)

Electro-magnetic techniques

Poor spatial resolution (esp. EEG)
Electromagnetic techniques

Main source of the signal: post-synaptic current flow along the dendrites of (pyramidal) neurons.

Temporal resolution: <1 ms

For the electric activity to be detected outside the skull, populations of neurons must fire in synchrony (50k for MEG, millions for EEG).
Electromagnetic techniques

An electric current creates a magnetic field around it

The right-hand rule:
Electromagnetic techniques

**EEG (electroencephalography):** electric potentials

**MEG (magnetoencephalography):** magnetic fields
Electromagnetic techniques

EEG electrodes on the scalp

MEG sensors outside the head, in a tank containing liquid helium to enhance superconductivity
MEG signal is dominated by currents oriented tangential to the skull.
Electromagnetic techniques

EEG picks up tangentially and radially oriented currents equally.

Currents oriented perfectly radial to the skull are missed in MEG. But there is very little signal that is so perfectly radial.
Electromagnetic techniques

MEG

EEG
EEG recordings by Hans Berger (circa 1925-1935)
EEG

Amplifier Bank

Electrode Array (e.g., n = 64)

Brain
Averaging over similar trials, Event Related Potentials (ERPs) have excellent temporal resolution (but coarse spatially).
Temporal and spatial resolution of EEG:

* Millisecond temporal resolution

* Localization of neural generators is complicated. Different tissues in the skull differ in their conductivities and electric potentials get distorted when passing through these structures)

* EEG + fMRI = powerful method to detect the precise timing and location of neural activity within the brain
MEG

Distribution of the magnetic field around the head tells you a lot about the underlying current generators.

Magnetic fields pass through skull and various tissues undistorted.

The main advantage over EEG: better spatial resolution (mm for cortex, worse for deeper sources).
The magnetic fields generated by neural activity are 100 million times smaller than the Earth’s magnetic field and 1 million times smaller than the magnetic fields produced in an urban environment.

**Problem:** magnetic fields generated by brain are 100 million times smaller than the Earth’s magnetic field

How do we pick up the tiny magnetic fields generated by the brain?
MEG

Solution part 1: magnetically shielded room
Solution part 2: superconductive sensors
MEG

Averaged response to 1 kHz tone
MEG

Averaged response to visual words

One can analyze the sensor data or the neural currents underlying the magnetic fields (inverse problem)
Whole brain imaging

Electrophysiology

Neuronal manipulation
Electrical properties (review)
Chapter 4

Electrophysiology

Now that we have reviewed the electrical properties of neurons and surveyed the equipment needed to study these properties, we will address the various electrophysiology techniques and how they are used.

Types of Electrophysiology Recordings

Electrophysiological recordings can be categorized into three main types based on the placement of the electrode in relation to the cell: (1) extracellular recordings; (2) intracellular recordings; and (3) patch clamp techniques (Figure 4.4).

Each technique can be used to address specific questions concerning the electrical properties of neurons. For example, questions regarding signals from neurons in vivo are most easily addressed using extracellular methods. Questions regarding the "open" and "closed" states of a specific ion channel in the presence of neuropeptide activators are best addressed using patch clamp techniques. Table 4.1 compares some of the questions that can be addressed using various types of electrophysiology recordings.

Three types of electrophysiology recordings (invasive)

Extracellular: outside the neuron

Intracellular: inside the neuron

Patch-clamp: adjacent to the membrane

Backbone of neuroscience research
Types of electrophysiology

Different types of recording capture different information and can answer different questions.

Extracellular Electrode

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<tr>
<th>Voltage Level</th>
<th>Extracellular</th>
<th>Intracellular</th>
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<tr>
<td>40 µV</td>
<td>40 mV</td>
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<td>20 µV</td>
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<td>0 µV</td>
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Extracellular: action potentials of groups of neurons + LFP

Intracellular: action potentials + EPSP + IPSP of a single cell
Extracellular recordings

Easier in vivo

Records a few tens up to hundreds neurons

Requires spike sorting to identify which cell fire which a.p.
Kristjan & Kristina (Working memory)

* Sample (visual recognition & memory encoding)

* Delay (memory maintenance)

* Test (visual recognition, comparison, decision making)
Whole brain imaging

Electrophysiology

Neuronal manipulation
Manipulating neurons

Some techniques perturb neural activity (inhibit or stimulate certain neurons) to test their role.

Types:
- Physical: cooling down a brain region to deactivate it
- Pharmacological: applying drugs to block channels
- Electrical: applying electrical currents to stimulate neurons
- Magnetic: applying magnetic fields (TMS)
- Optic: laser (optogenetics)
Transcranial Magnetic Stimulation (TMS)

TMS allows transient* and safe* disruption of local neural activity, in effect creating reversible lesions (loss-of-function and gain-of-function experiments).
Optogenetics: a light switch for the brain

It allows the millisecond-precise control of selected groups of neurons
CLARITY: the future to visualize brain structure?
Overview
Summary

- Structural (functional) brain imaging capture the anatomy (activation) of different brain regions.
- MRI (fMRI) technique of choice for good spatial resolution.
- EEG and MEG have excellent temporal resolution.
- Electrophysiology techniques measure activity at the neuron level.
- No perfect technique allows yet to monitor extensive regions of brain circuits with a single-neuron resolution.
To know more

Chapters 1 and 4
Guide to research techniques in neuroscience,
Matt Carter and Jennifer Shieh,
Academic Press, 2010
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