How to study the brain?

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Neurological diseases and cases

Stroke

Alzheimer’s Disease

Parkinson’s Disease

Patient Leborgne (“Tan”)

Phineas Gage

Patient HM
Methods to study the brain and its role in behaviour/cognition

- Behavioural studies
- Manipulations of brain function
- Neuroanatomy and histology
- Electrophysiology
- Imaging (MRI and PET)
- Computational models/ brain-based devices
- Etc.!!

Understanding of brain-behaviour relations requires combination of many different methodological approaches (multidisciplinarity)!
Case studies: Patient H.M.

Thorough behavioural and cognitive analysis:
- striking impairments in specific types of memory, including aspects of declarative and spatial memory;
- other cognitive and memory functions were largely unaffected.


HM’s obituary: [http://www.nytimes.com/2008/12/05/us/05hm.html](http://www.nytimes.com/2008/12/05/us/05hm.html)
Figure 3. A Taxonomy of Mammalian Memory Systems
This taxonomy lists the brain structures and connections thought to be especially important for each kind of declarative and nondeclarative memory.
Experimentally induced lesions and other brain manipulations

- Selective destruction of specific brain sites (mechanical, electrolytic, neurotoxic)
- Temporary pharmacological manipulations via pre-implanted micro-cannulae to switch neurons or specific receptors on and off
- Electrical stimulation of specific brain sites
- Targeted mutations of brain-specific genes
- Optogenetics
- Trans-cranial magnetic stimulation (TMS)

Stereotactic brain surgery in anaesthetized rat

Optogenetics

Method of the year 2010
http://www.nature.com/nmeth/journal/v8/n1/full/nmeth.f.322.html
Selective place learning deficits after hippocampal lesions in rats

Search preference for target region during 'probe' trials (▲)

The discussed lesion studies suggest that:

a) The hippocampus is necessary for spatial and declarative memory.

b) The hippocampus is sufficient for such memory.

c) Both a) and b).

d) None of the above.
Neuroanatomical study of brain connectivity

- Neuronal tract tracing

  PHA-L is injected into a region of the brain and taken up by dendrites and cell bodies.

  PHA-L is transported by axoplasmic flow.

  Axons and terminal buttons can be seen under the microscope.

- Diffusion magnetic resonance imaging (Berg-Johansen & Rushworth, 2009, Ann Rev Neurosci 32:75-94)
Polymodal sensory input to the hippocampus

Hippocampus

Electrophysiology: Recording the electrical activity of the brain

• Single-unit recordings: recording the electrical activity of single neurons

Example – ‘Place cells’ in the hippocampus

• Local field potential (LFP) recordings: recording electrical potentials generated by many neurons (‘field potentials’)

Example – LFP recorded from rat hippocampus

www.nobelprize.org/nobel_prizes/medicine/laureates/2014/okeefe-lecture.html
Electrophysiology in humans

• **Invasive single-unit and EEG recordings**
  Only conducted in rare cases for the pre-surgical evaluation of epilepsy patients (Engel et al., 2005, Nature Rev Neurosci 6:35-47)

• **Surface EEG**
  Spontaneous and event-related (evoked)

• **Magnetencephalography (MEG)**
  - Measures the small magnetic-field changes accompanying electrical voltage changes due to brain activity
  - Better spatial resolution than EEG (<1 cm)
Magnetic Resonance Imaging (MRI)

Images are generated from magnetic-resonance (MR) signal that emanates from hydrogen nuclei in brain tissue when these are aligned by a strong magnetic field and then excited by a magnetic pulse.

- **Structural MRI of the brain**
  Non-invasive imaging of brain structure based on MRI contrast between different tissue types due to different densities of H nuclei

- **Functional MRI of the brain**
  Non-invasive imaging of brain ‘activity’ based on MR signal changes associated with metabolic and cerebral-blood-flow changes. Most common method is based on changes in the Blood-Oxygen-Level-Dependent (BOLD) MR signal.

http://www.scholarpedia.org/article/MRI
http://www.scholarpedia.org/article/Functional_magnetic_resonance_imaging
Sir Peter Mansfield, FRS
1933 – 2017

School of Physics, University of Nottingham

Nobel Prize in Physiology or Medicine 2003 (shared with Paul Lauterbur)

For discoveries concerning MRI

http://nobelprize.org/nobel_prizes/medicine/laureates/2003/
Activation of the human hippocampus during place memory task in a virtual environment: an fMRI study

The discussed fMRI study suggests that:

a) The hippocampus is necessary for place memory.

b) The hippocampus is sufficient for such memory.

c) Both a) and b).

d) None of the above.
Positron Emission Tomography (PET)

Involves injection of radioactive tracers that resemble compounds of biological interest (e.g., $^{18}$F-2-deoxyglucose). Using dedicated detectors around the head, these tracers can be followed in the brain (e.g., to monitor metabolic activation).

**PET imaging of brain activity and chemical neurotransmission**

_Volkow et al., 1996, J Nucl Med 37:1242-1254._

**Changes in Parkinson’s**

Less DAT in striatum – reflects degeneration of dopaminergic fibres that express this transporter at terminals.

More binding of dopamine receptor-specific tracer – reflects less dopamine release that could displace tracer from receptor.

Some regions hypo-, others hyperactive; changes across disease course.
Modeling the brain: Spatial learning and navigation by Darwin X, a brain-based device

Darwin X and its simulated brain

Spatial memory task

Spatial learning

Place-specific firing in simulated hippocampus

How to Study the Brain? – Selected Reading

Textbook chapter:

Review article:

Book (for bedside reading):
How to Study the Brain? – Some questions to think about

General

• Is there an ideal method to study the brain?
• What are the pros and cons of the different methods (consider invasiveness, spatial and temporal resolution, type of information yielded, sensitivity, etc.)?
• What are the ethical problems of brain research in animals and humans?

Specific

• If a lesion of a brain area results in loss of a specific behavioural or cognitive function, does this mean the brain area is necessary for this function?
• Does it mean other brain areas do not contribute to this function?
• If imaging or electrophysiological methods indicate that ‘activation’ of a brain area correlates with a given cognitive function, does this mean the brain area is necessary for this function?
• If imaging or electrophysiological methods indicate NO ‘activation’ of a brain area during a given cognitive function, does this mean the brain area is not involved in this function? (Consider the issues of sensitivity and of ‘negative’ findings.)