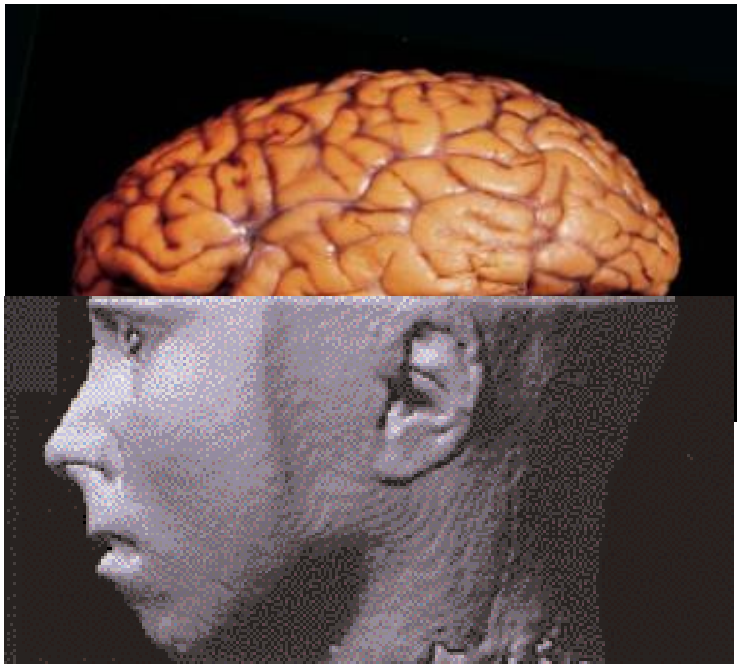
C84NAB: Neuroscience and Behaviour

How to study the brain?

Tobias Bast, School of Psychology, University of Nottingham

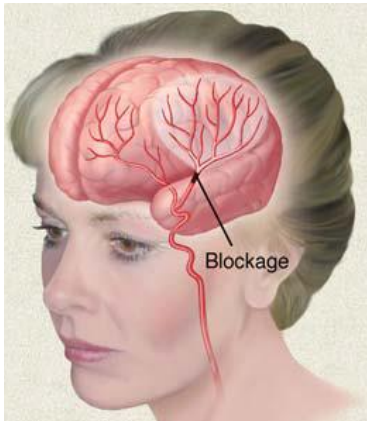


The University of Nottingham

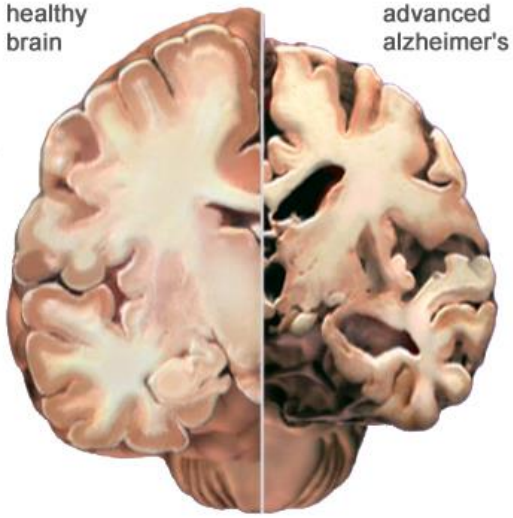
UNITED KINGDOM · CHINA · MALAYSIA

Neurological diseases and cases

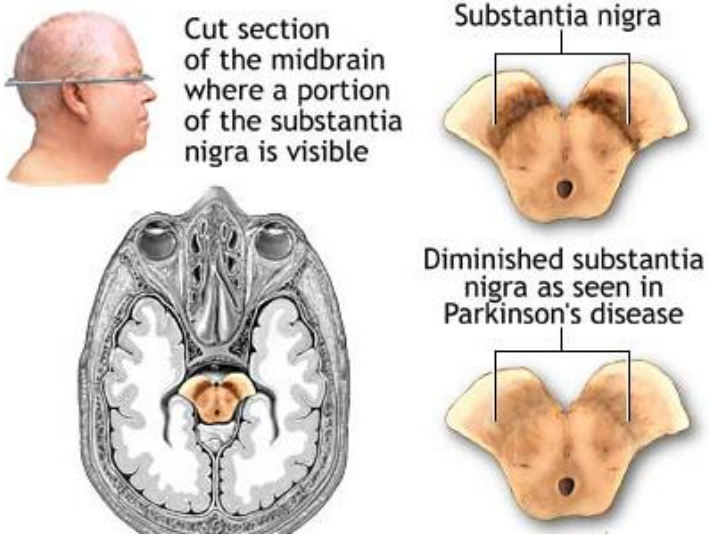
Stroke



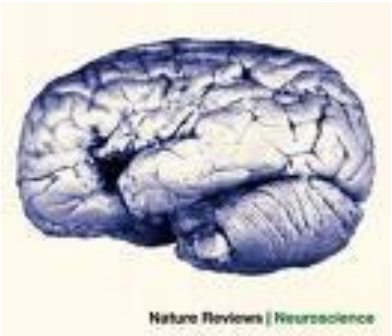
Alzheimer's Disease



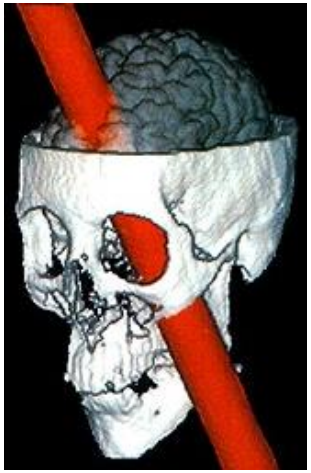
Parkinson's Disease



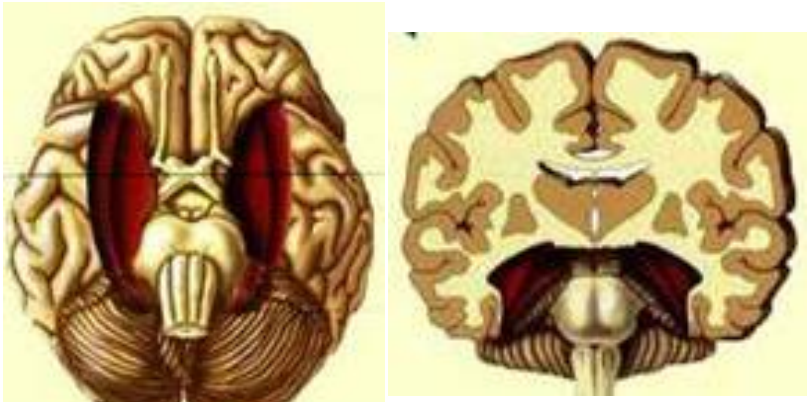
Patient Leborgne ("Tan")



Phineas Gage

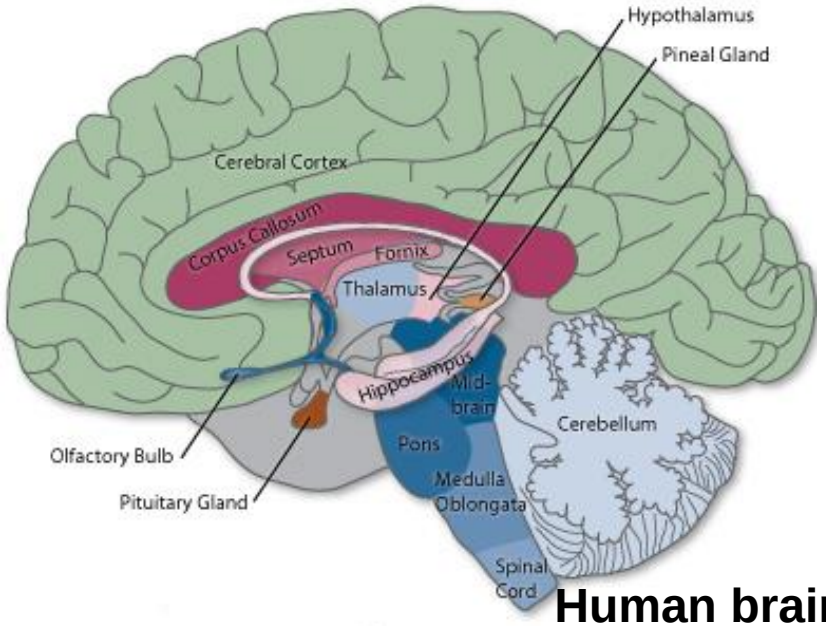


Patient HM

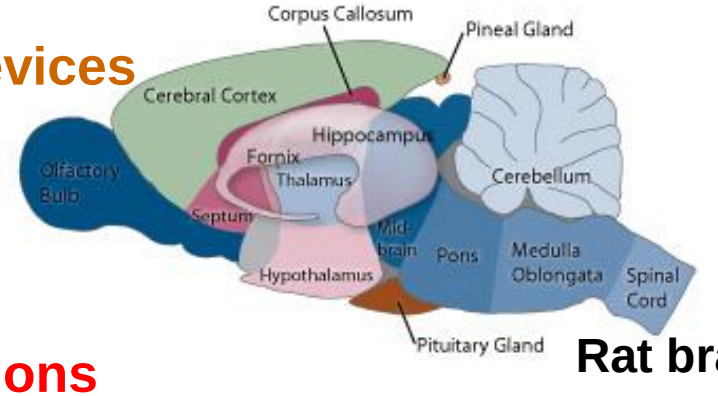


Methods to study the brain and its role in behaviour/cognition

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



Human brain

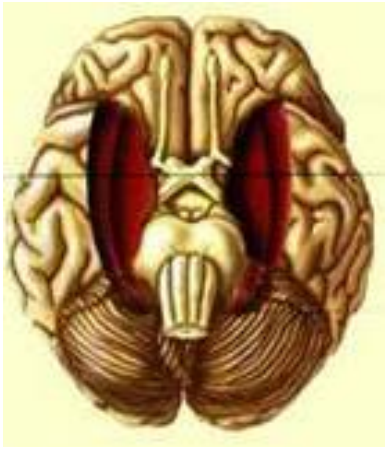


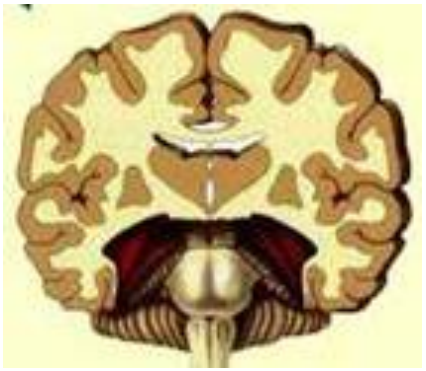
Rat brain

Understanding of brain-behaviour relations requires combination of many different methodological approaches (multidisciplinarity)!

Case studies: Patient H.M.

Henry G. Molaison
1926-2008





Surgical resection of medial temporal lobe, mainly hippocampus, to stop epileptic seizures

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.**

Corkin (2002) *Nature Neurosci Rev* 3:153

HM's obituary: http://www.nytimes.com/2008/12/05/us/05hm.html

Concept of memory systems

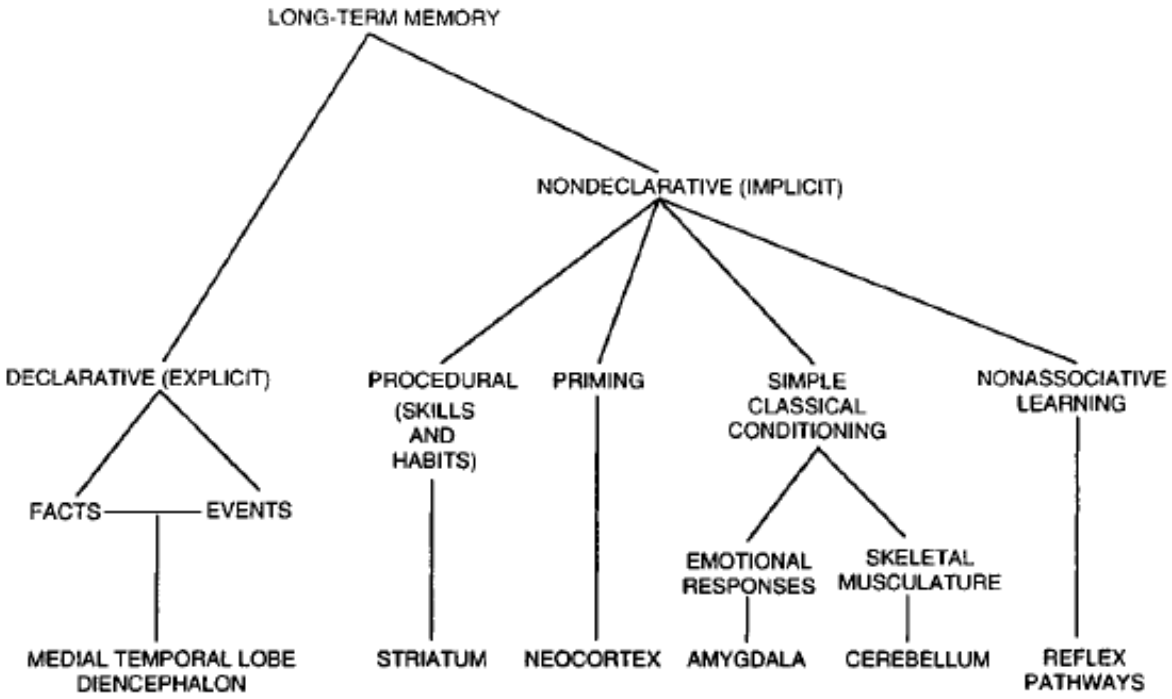


Figure 3. A Taxonomy of Mammalian Memory Systems

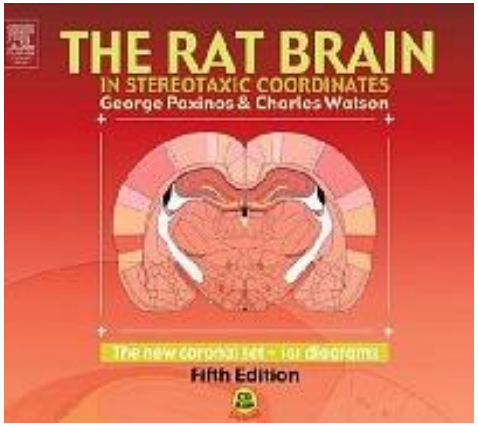
This taxonomy lists the brain structures and connections thought to be especially important for each kind of declarative and nondeclarative memory.

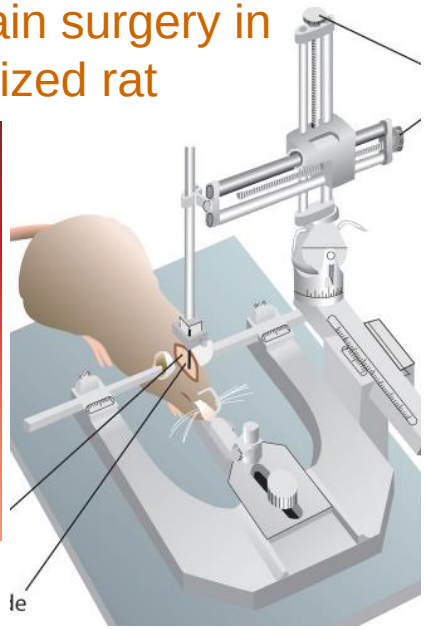
Milner et al. (1998) Cognitive neuroscience and the study of memory. *Neuron* 20:445-468.

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

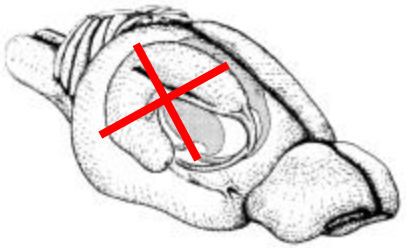
Method of the year 2010
http://www.nature.com/nmeth/journal/v8/n1/full/nmeth.f.322.html

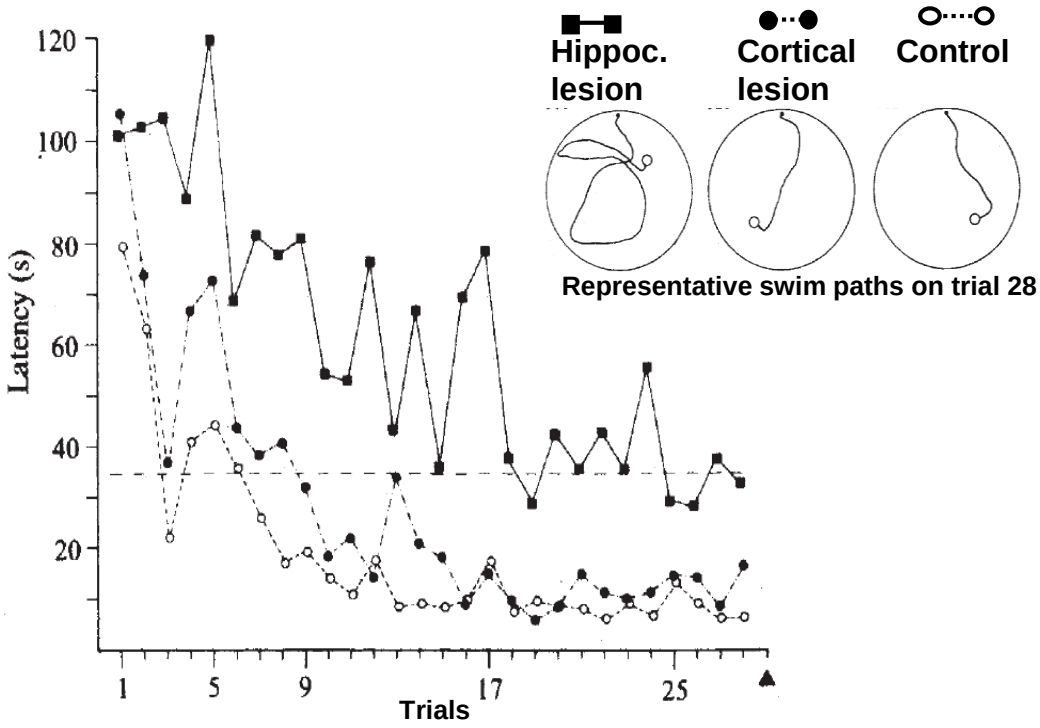
TMS

Selective place learning deficits after hippocampal lesions in rats

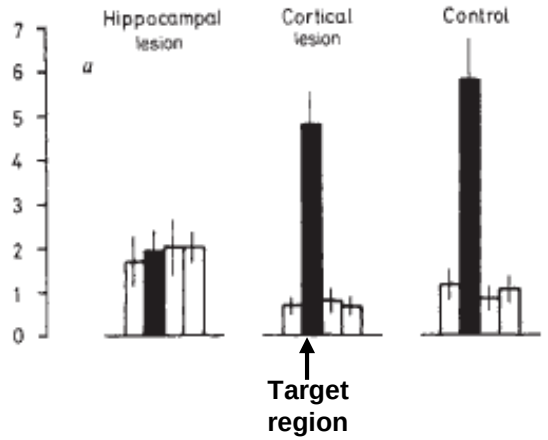
Watermaze

Hippocampal lesion





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



RGM Morris et al (1982) *Nature* 297:681

The discussed lesion studies suggest that:

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

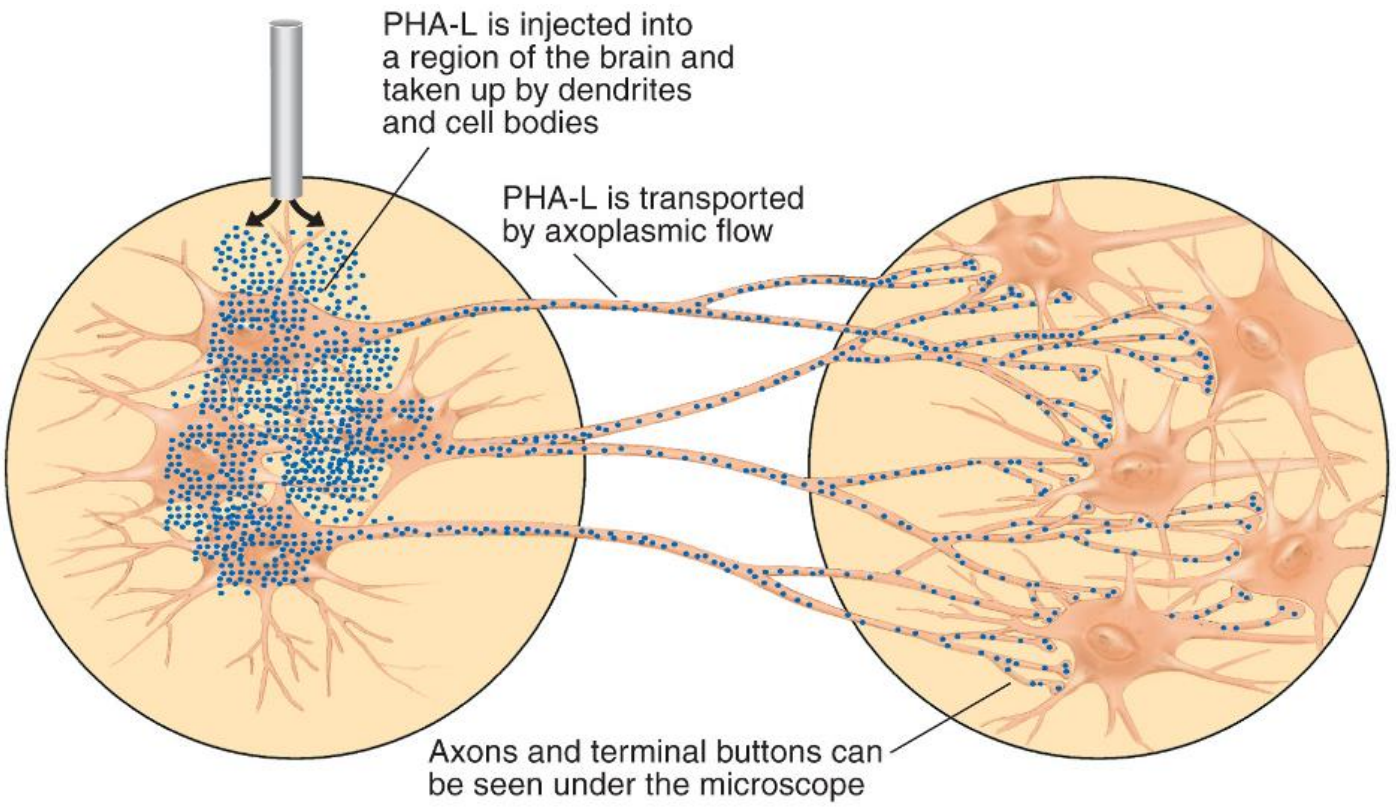
b) **The hippocampus is sufficient for such memory.**

c) **Both a) and b).**

d) **None of the above.**

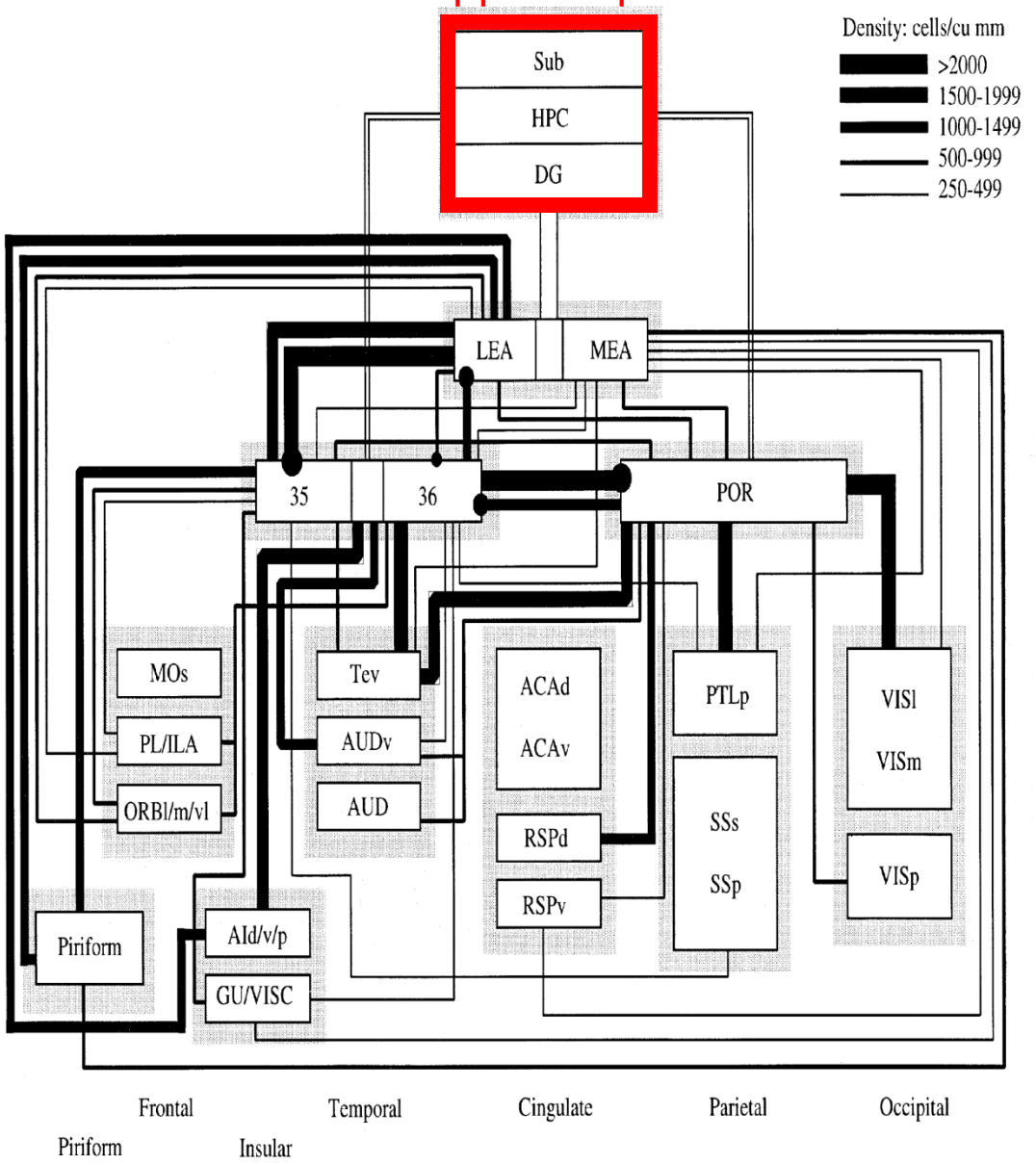
Neuroanatomical study of brain connectivity

- Neuronal tract tracing



- Diffusion magnetic resonance imaging (Berg-Johansen & Rushworth, 2009, Ann Rev Neurosci 32:75-94)

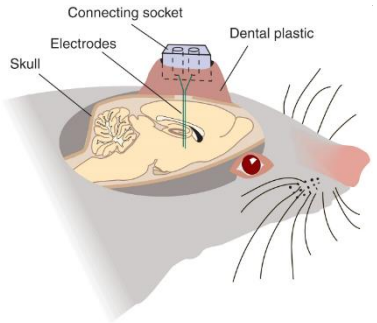
Polymodal sensory input to the hippocampus



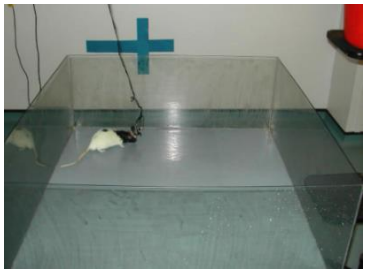
Burwell (2000) The parahippocampal region: cortico-cortical connectivity. *Ann NY Acad Sci* 911:25-42.

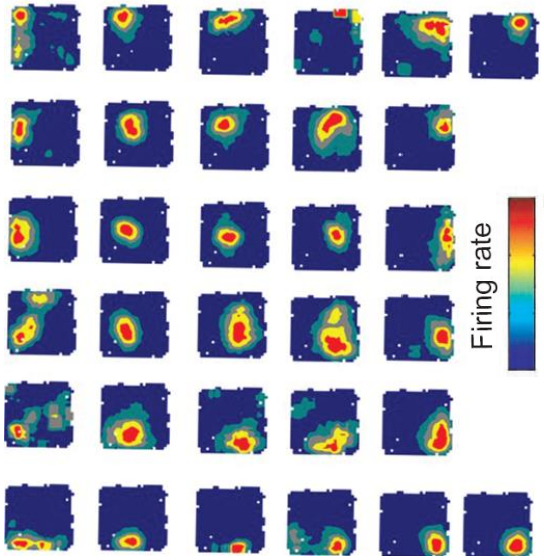
Electrophysiology: Recording the electrical activity of the brain

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



Example – 'Place cells' in the hippocampus



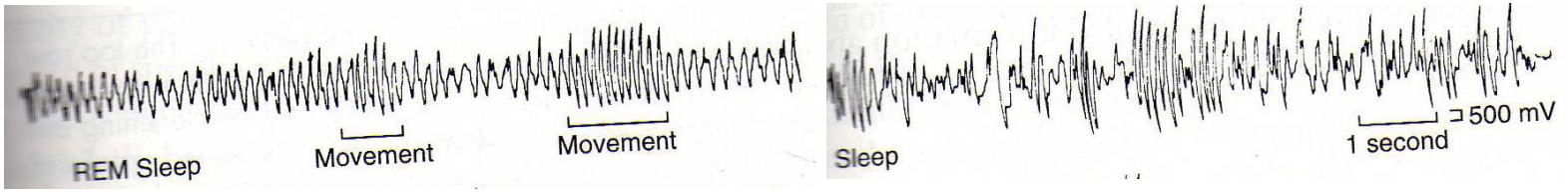


Nobel Prize Physiology & Medicine 2014

J O´Keefe (2014) Nobel Lecture: Spatial Cells in the Hippocampal Formation
www.nobelprize.org/nobel_prizes/medicine/laureates/2014/okeefe-lecture.html

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

Example – LFP recorded from rat hippocampus



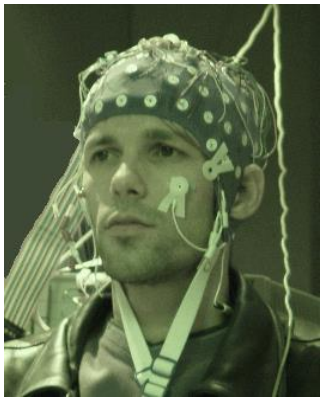
Electrophysiology in humans

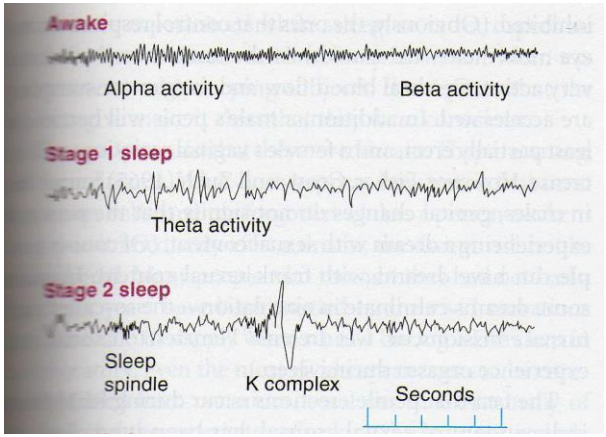
- **Invasive single-unit and EEG recordings**

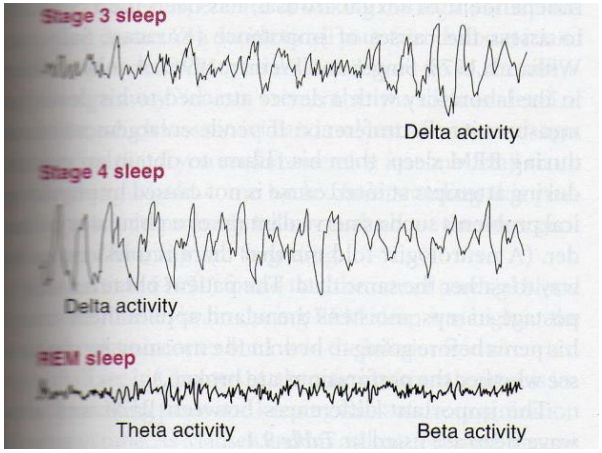
  Only conducted in rare cases for the pre-surgical evaluation of epilepsy patients (Engel et al., 2005, Nature Rev Neurosci 6:35-47)

- **Surface EEG**

  Spontaneous and event-related (evoked)

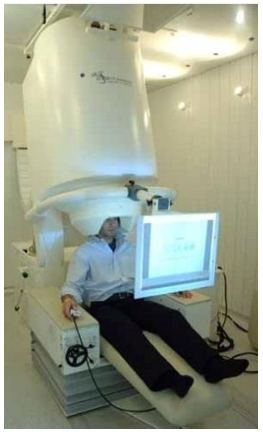






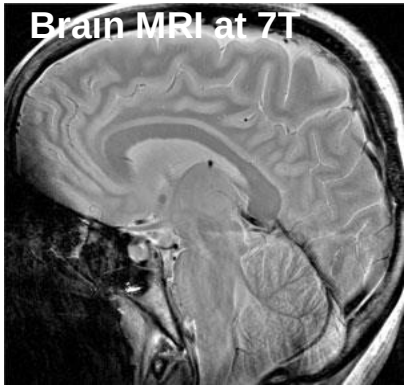
- **Magnetencephalography (MEG)**

- 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.

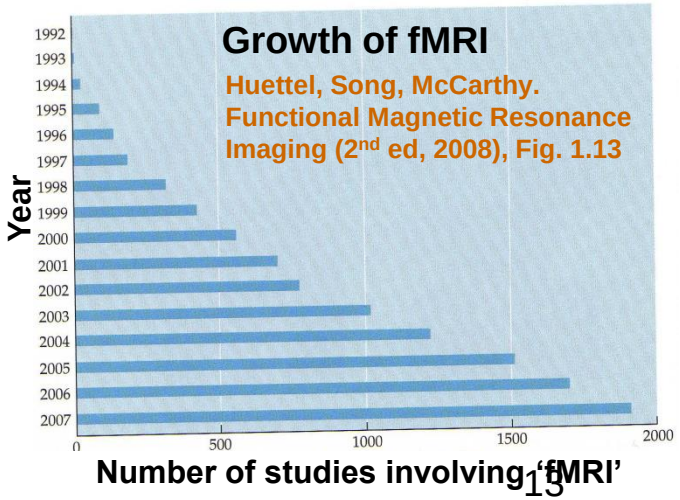


- **Structural MRI of the brain**

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 **B**lood-**O**xygen-**L**evel-**D**ependent (**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

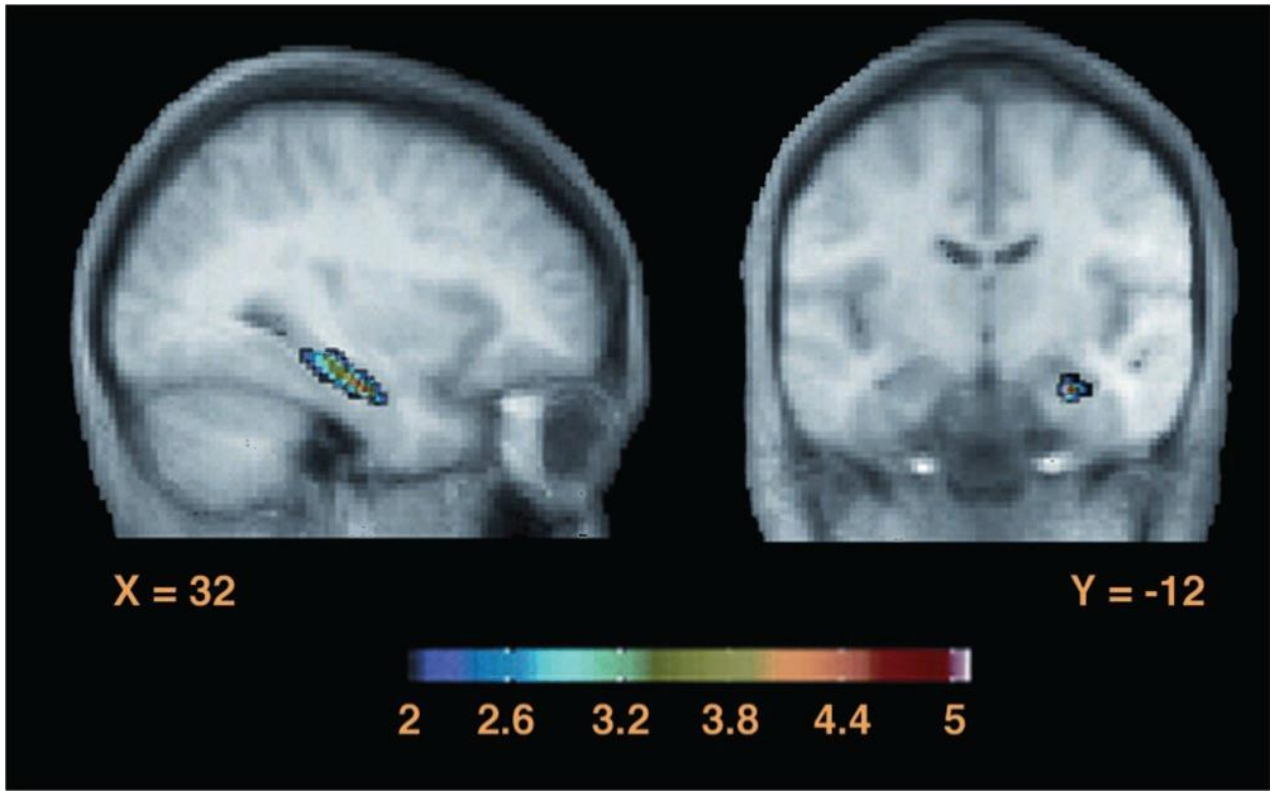
Nobel Prize in Physiology or Medicine 2003 (shared with Paul Lauterbur)

For discoveries concerning MRI

http://nobelprize.org/nobel_prizes/medicine/laureates/2003/

https://www.theguardian.com/science/2017/feb/20/sir-peter-mansfield-obituary

Activation of the human hippocampus during place memory task in a virtual environment: an fMRI study



Bohbot et al. (2004) Hippocampal function and spatial memory: . . .. *Neuropsychology* 18:418-425.

The discussed fMRI study suggests that:

a) The hippocampus is necessary for place memory.

b) The hippocampus is sufficient for such memory.

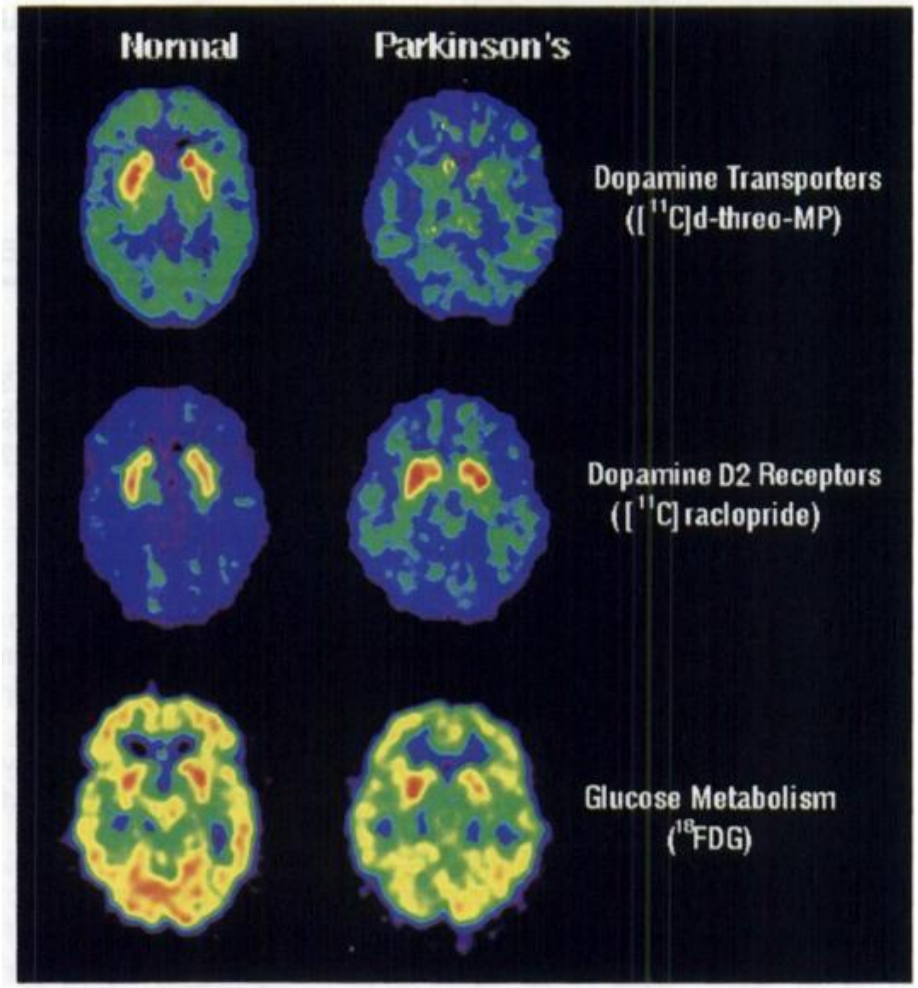
c) Both a) and b).

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

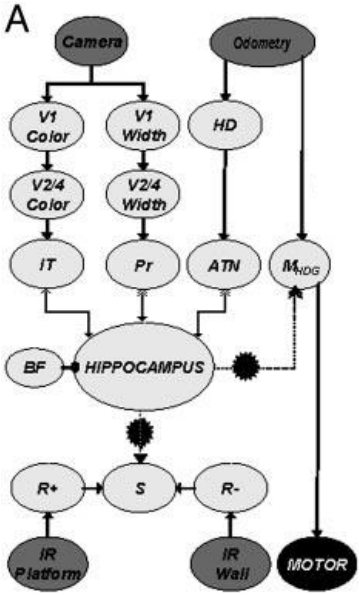
Less DAT in striatum – reflects degeneration of dopaminergic fibres that express this transporter at terminals

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

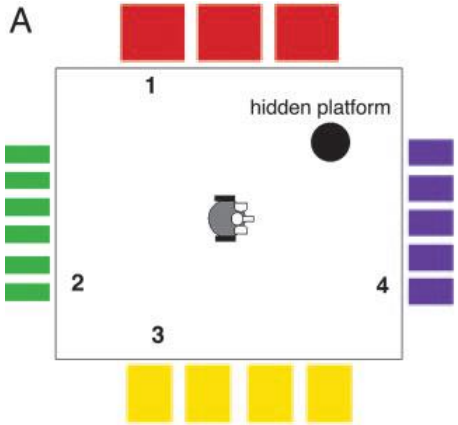
Some regions hypo-, others hyperactive; changes across disease course

Modeling the brain: Spatial learning and navigation by Darwin X, a brain-based device

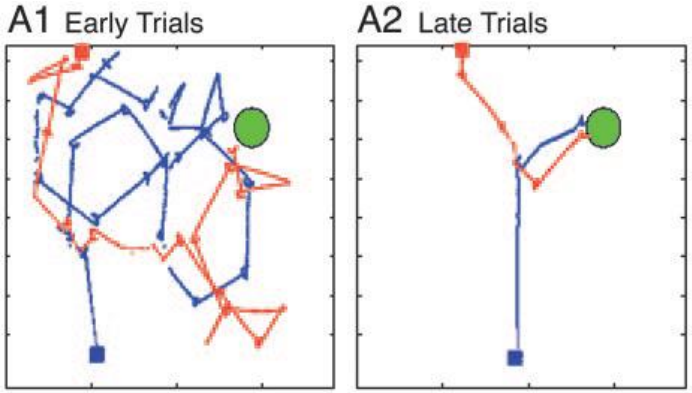
Darwin X and its simulated brain



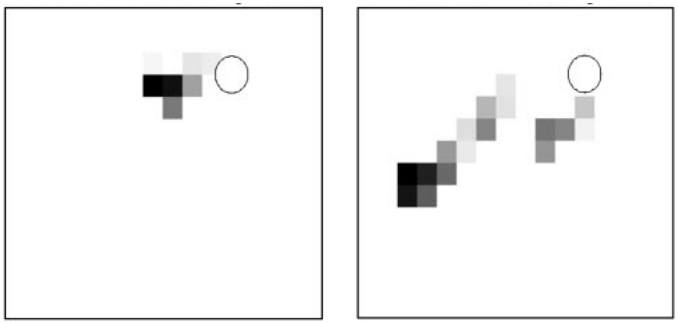
Spatial memory task



Spatial learning



Place-specific firing in simulated hippocampus



Krichmar et al. (2005) Characterizing functional hippocampal pathways in a brain-based device as it solves a spatial memory task. *Proc Nat Acad Sci USA* 102:2111-2116.

How to Study the Brain? – Selected Reading

***Textbook chapter*:**

Carlson NR (any recent edition) The physiology of behavior. Chapter 5, *Methods and strategies of research*.

***Review article*:**

Milner B, Squire LR, Kandel ER (1998) Cognitive neuroscience and the study of memory. *Neuron* 20:445-468.

***Book (for bedside reading)*:**

Corkin S (2014) Permanent present tense: The man with no memory, and what he taught the world. Penguin Books: London.

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.)