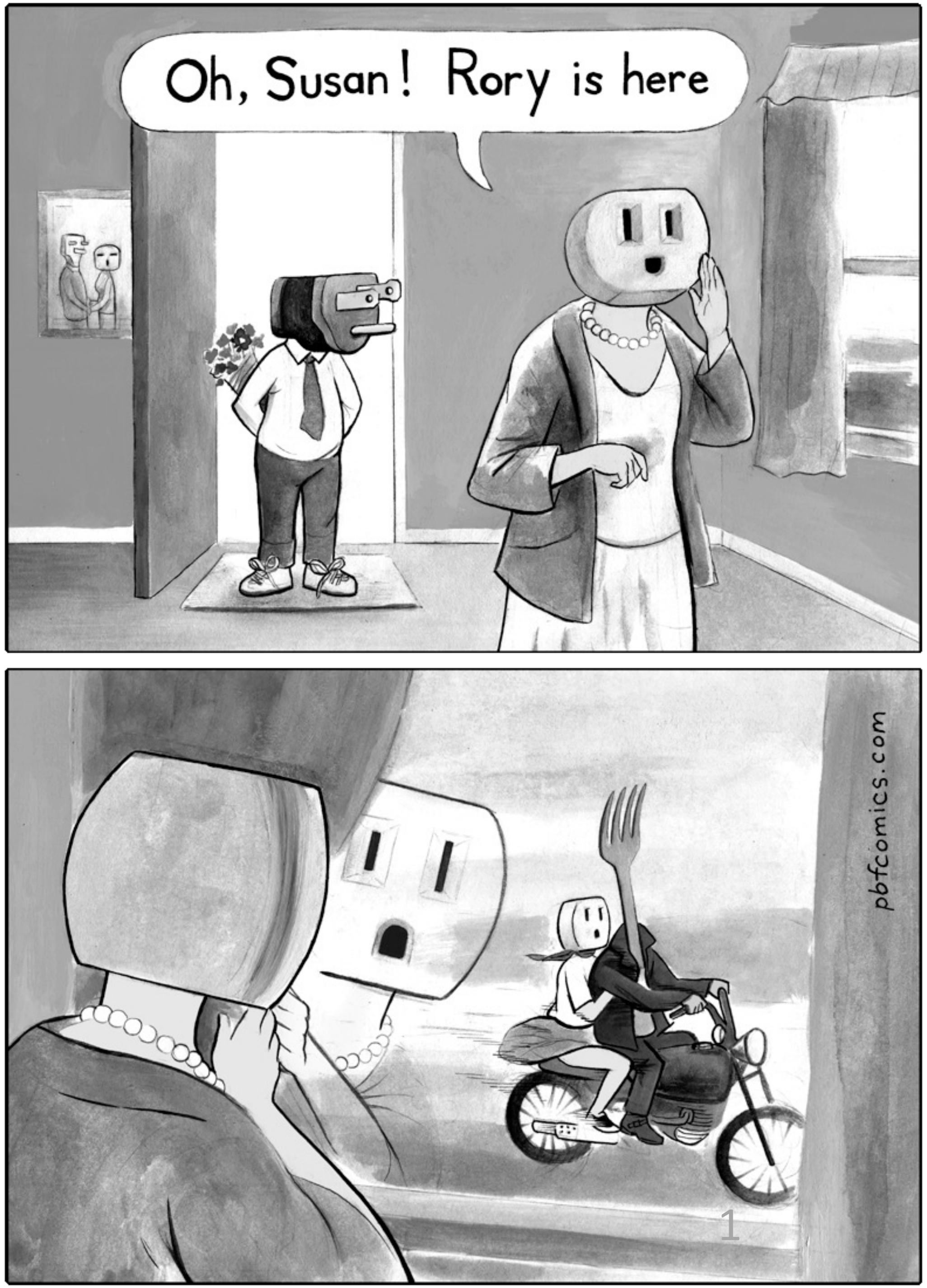
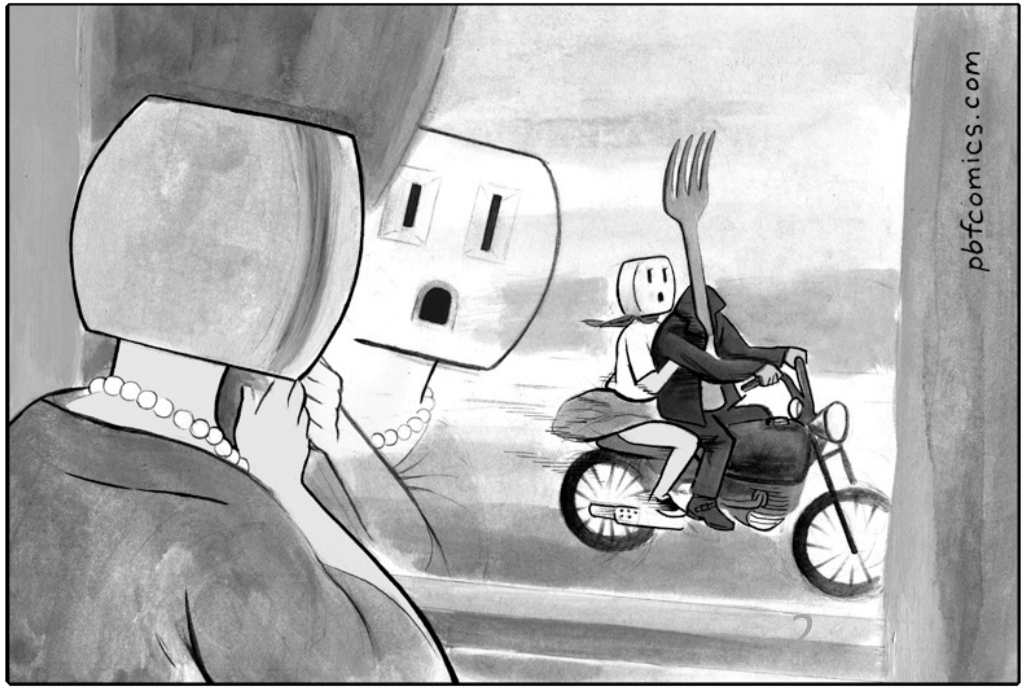
PSYC 304

Tools in neuroscience research

Jay Hosking, PhD



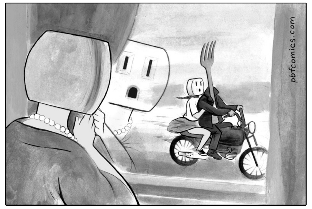
A. Methodological considerations
B. Recording the brain's electrical activity
C. Animal models and methods
D. Structural and functional neuroimaging
E. Thinking critically, using fMRI as a case study
F. An "assignment"



Lecture overview

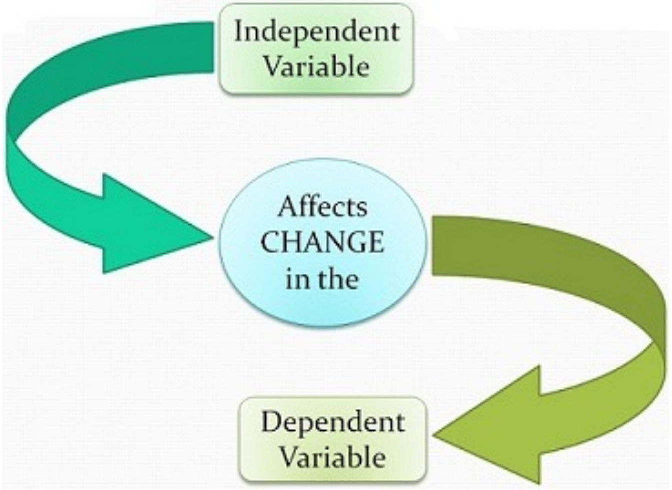
1. What do researchers mean when they state “there is no one ideal method to answer the questions in neuroscience”?
2. Describe three basic experimental designs for studying the relationship between brain and behaviour. What advantages do each design confer? What limitations are associated with each?
3. Describe three methods for recording the brain’s electrical activity, including their benefits and drawbacks.
4. What is the “Halle Berry neuron”? What commonly held idea does it refute? What does it suggest about brain and behaviour?
5. What are the benefits of using animal models? How is cognition operationalized in animal models? Compare some methods that can be used to probe brain and behaviour.
6. Describe and compare the different methods of structural brain imaging that are listed in this lecture.
7. Explain how an MRI machine works.
8. Describe and compare the different methods of functional brain imaging that are listed in this lecture.
9. Explain how PET and fMRI work.
10. Discuss the various theoretical issues involved in interpreting functional brain imaging data.
11. Why might “a multi-methodological approach” often be the best answer to how to approach a research question in behavioural neuroscience?

Learning objectives



How do we infer the relationship between brain and behaviour?

In other words, how do we design an experiment in behavioural neuroscience?



Most common approaches:

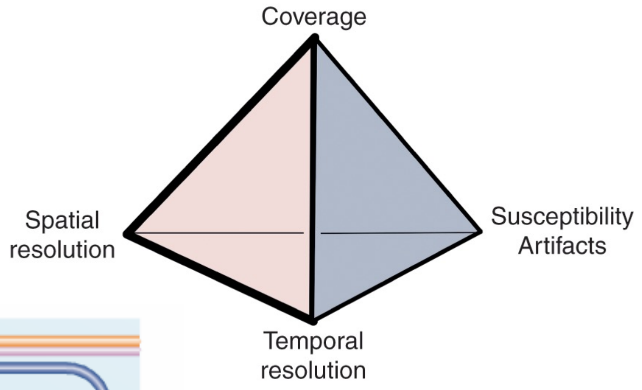
- **Induce a loss of function**
- **Induce a gain of function**
- **Monitor behaviour and brain activity simultaneously**

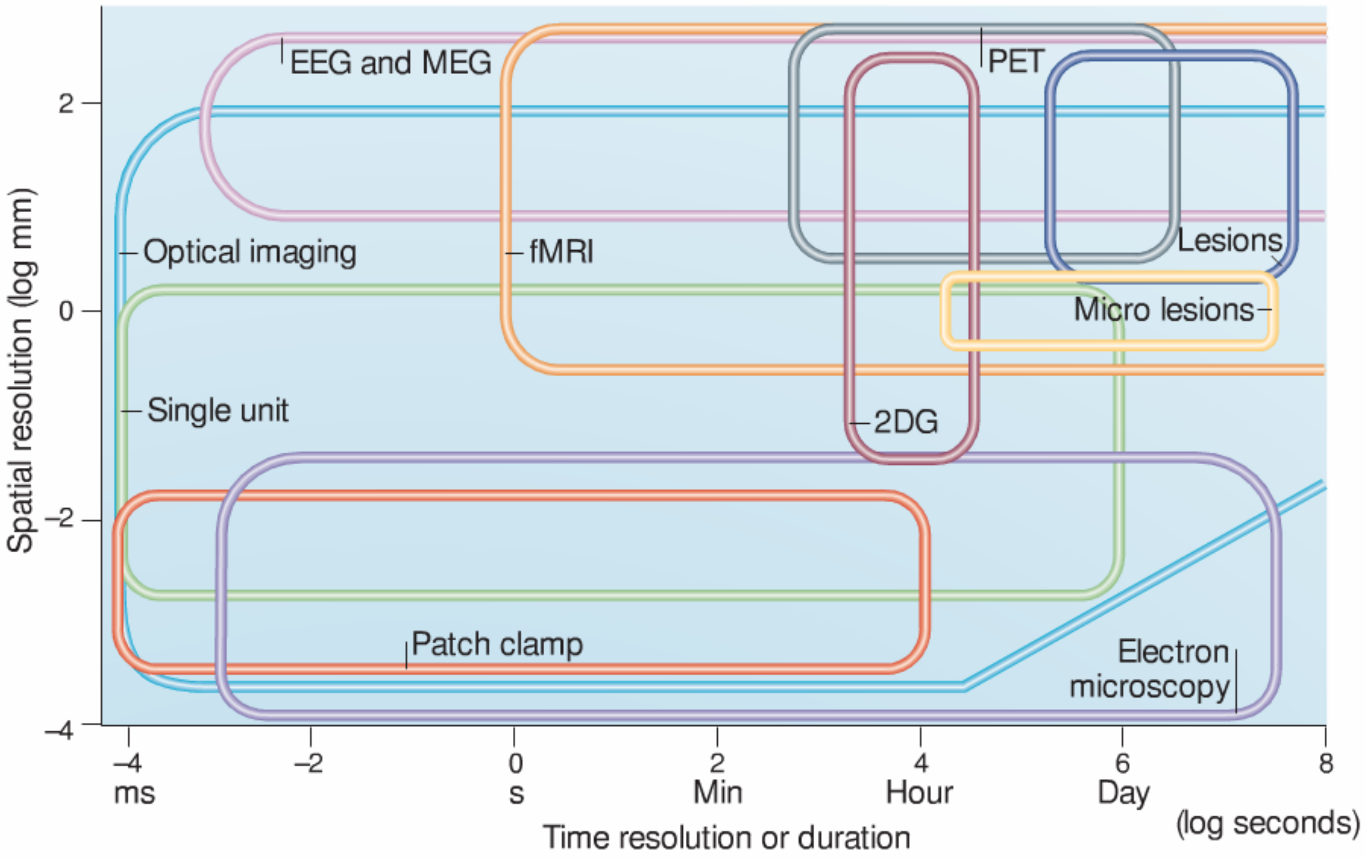
Each has considerations and limitations

Again, sometimes a true experiment isn't feasible

No one ideal method

- Scales
- Trade-offs





The following is a non-exhaustive list of methods!

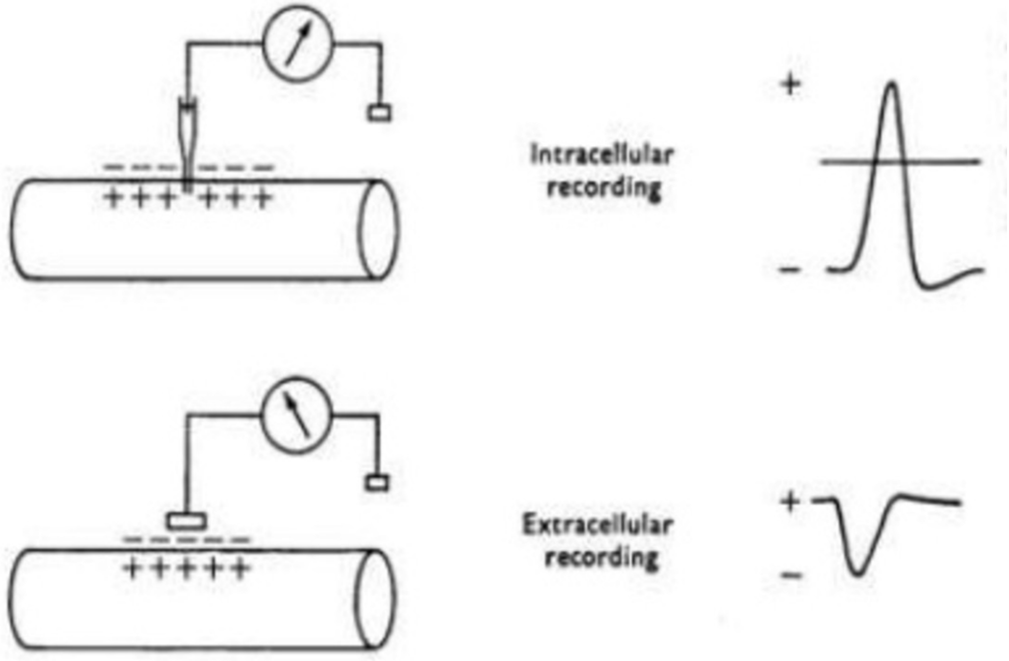
Recording the brain's electrical activity

- Single-cell recording
- Electroencephalography (EEG)
- Event-related potentials (ERP)

Electrical activity

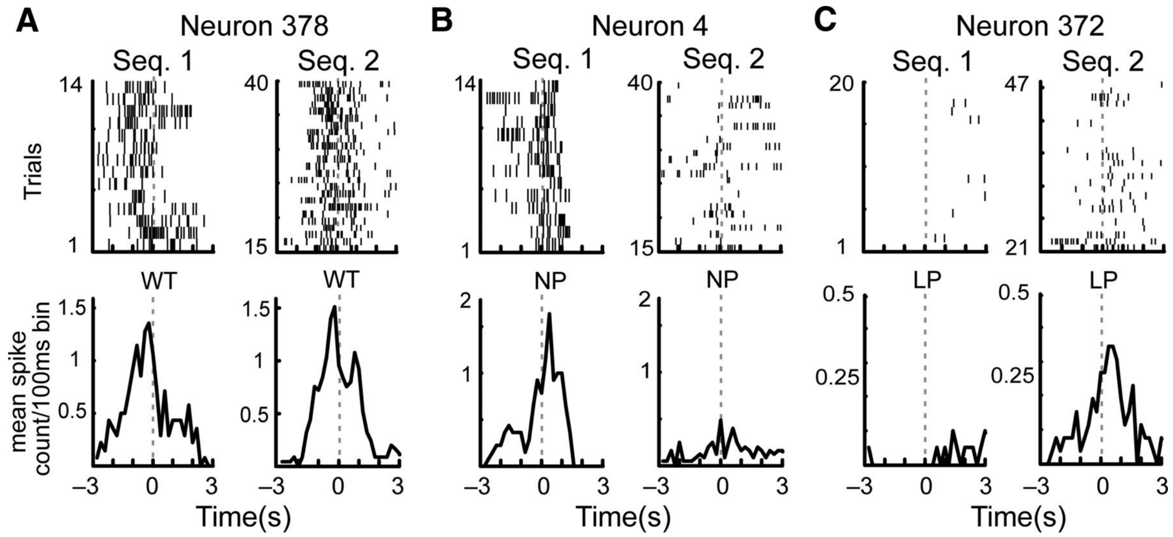
Single-cell recording

- Intracellular
- Extracellular

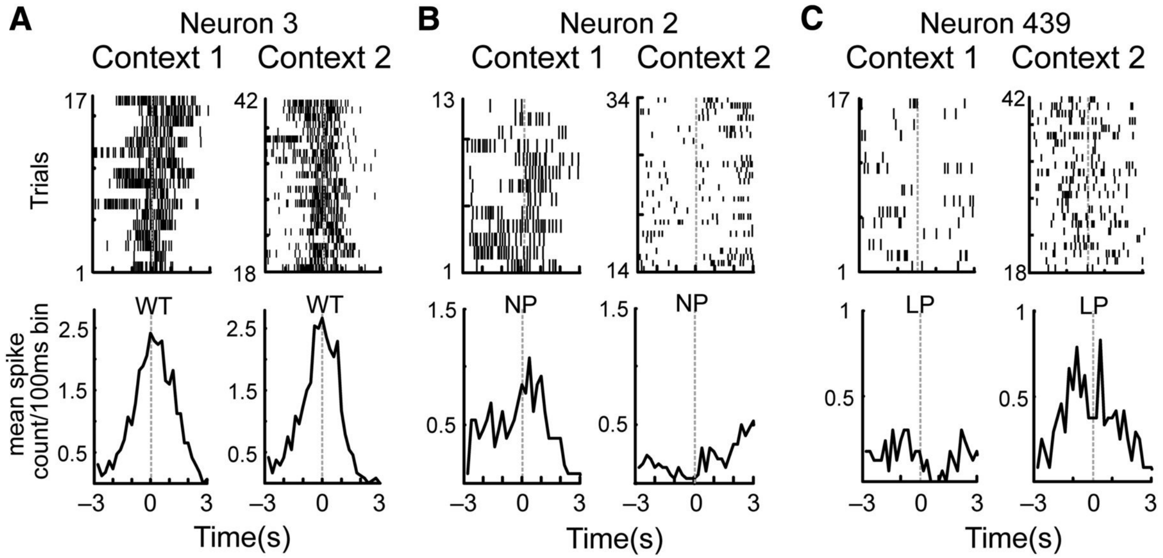


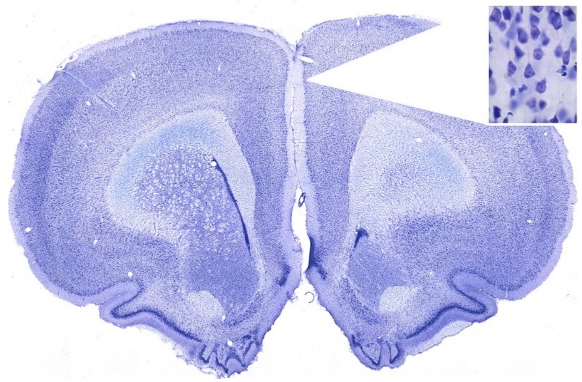
Single-cell recording: what does it mean?

- i.e. Firing patterns
  - Raster plots
- Population coding



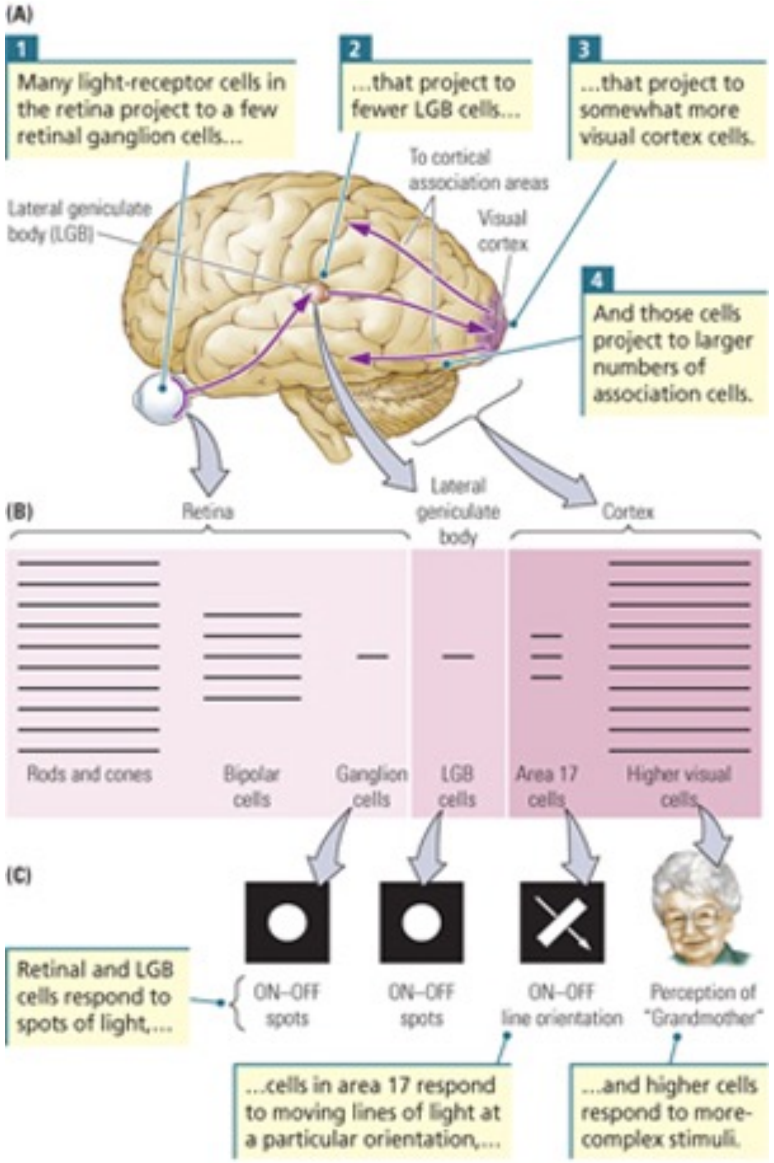
Ma *et al.* 2016, JNeuro





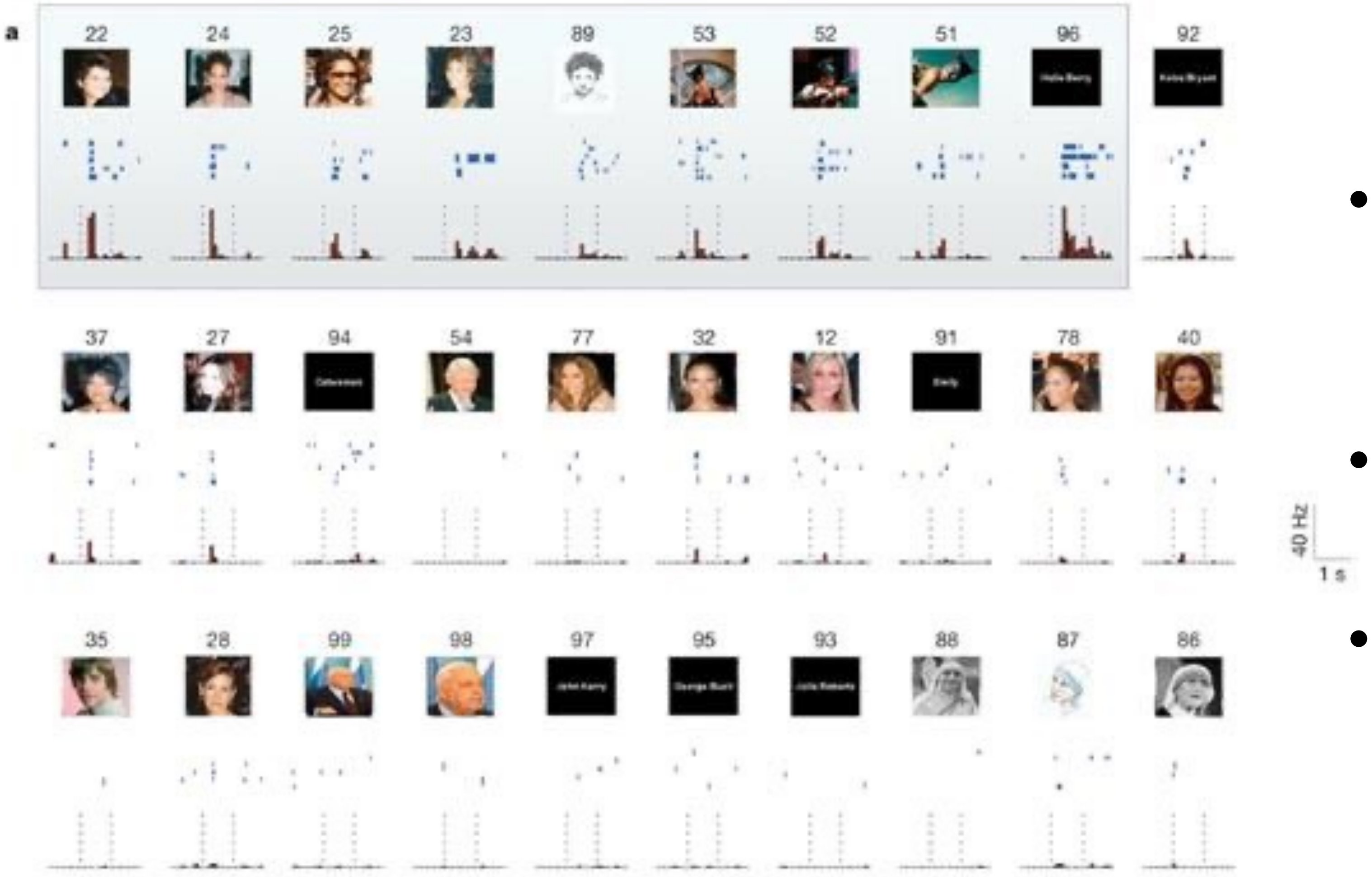
Electrical activity

Convergence and divergence



- Parallel processing
- Distributed representations
- Population coding
- But…

The Halle Berry neuron?

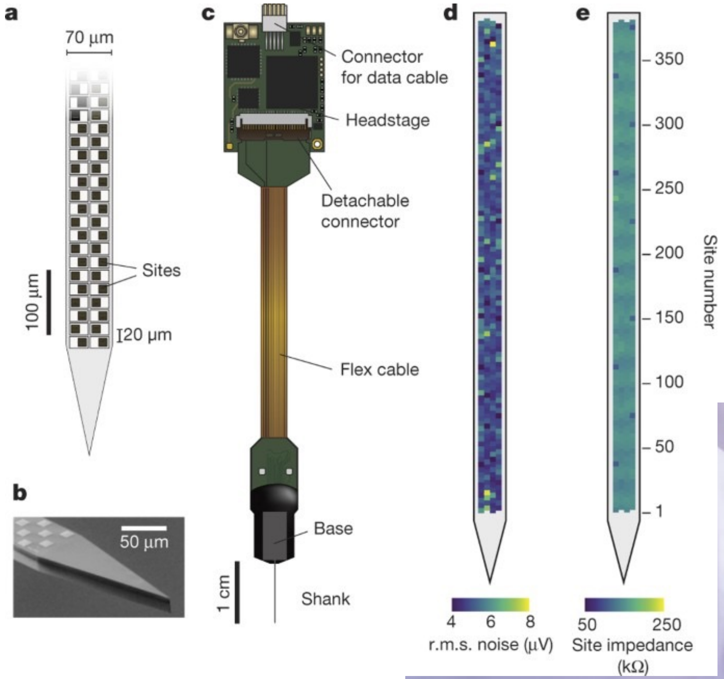


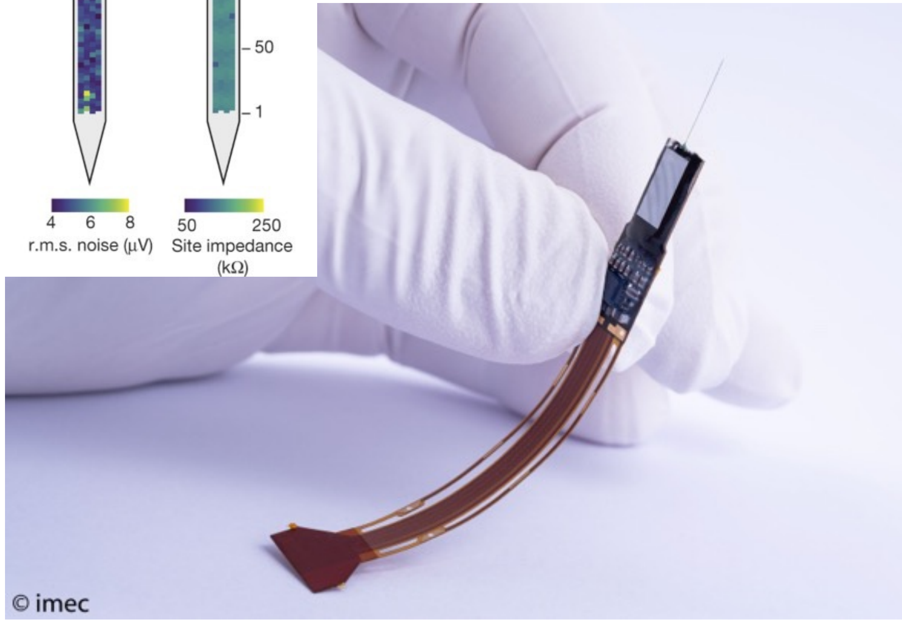
- See also: Batman, Sidney Opera House (or similar?), Jennifer Aniston
- Some high convergence in the brain
- Probably still involved in other population coding (let's hope so!)

Quiroga *et al.*, 2005

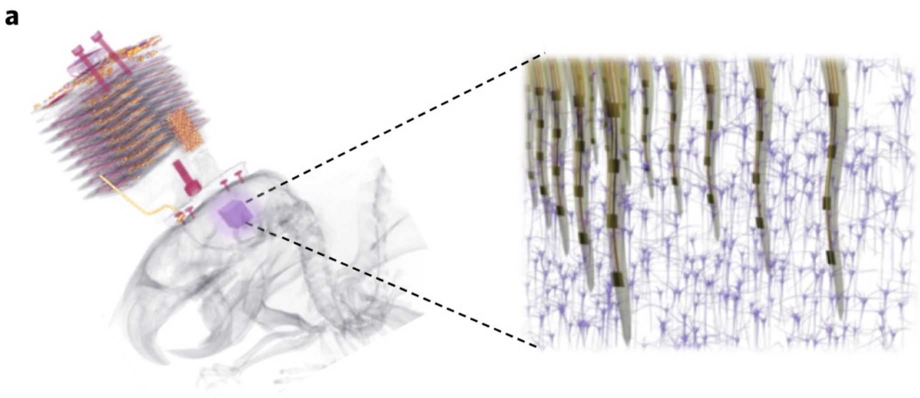
Two main limitations to directly recording electrical activity

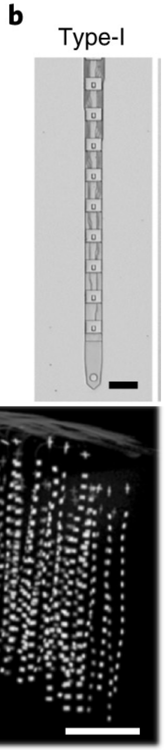
1. Getting more electrodes into the brain
2. Making sense of tremendous amounts of data





Jun *et al.*, 2017



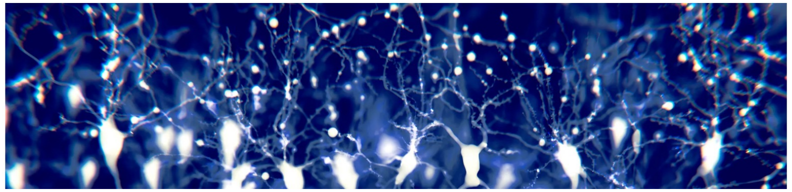


Zhao *et al.*, 2022

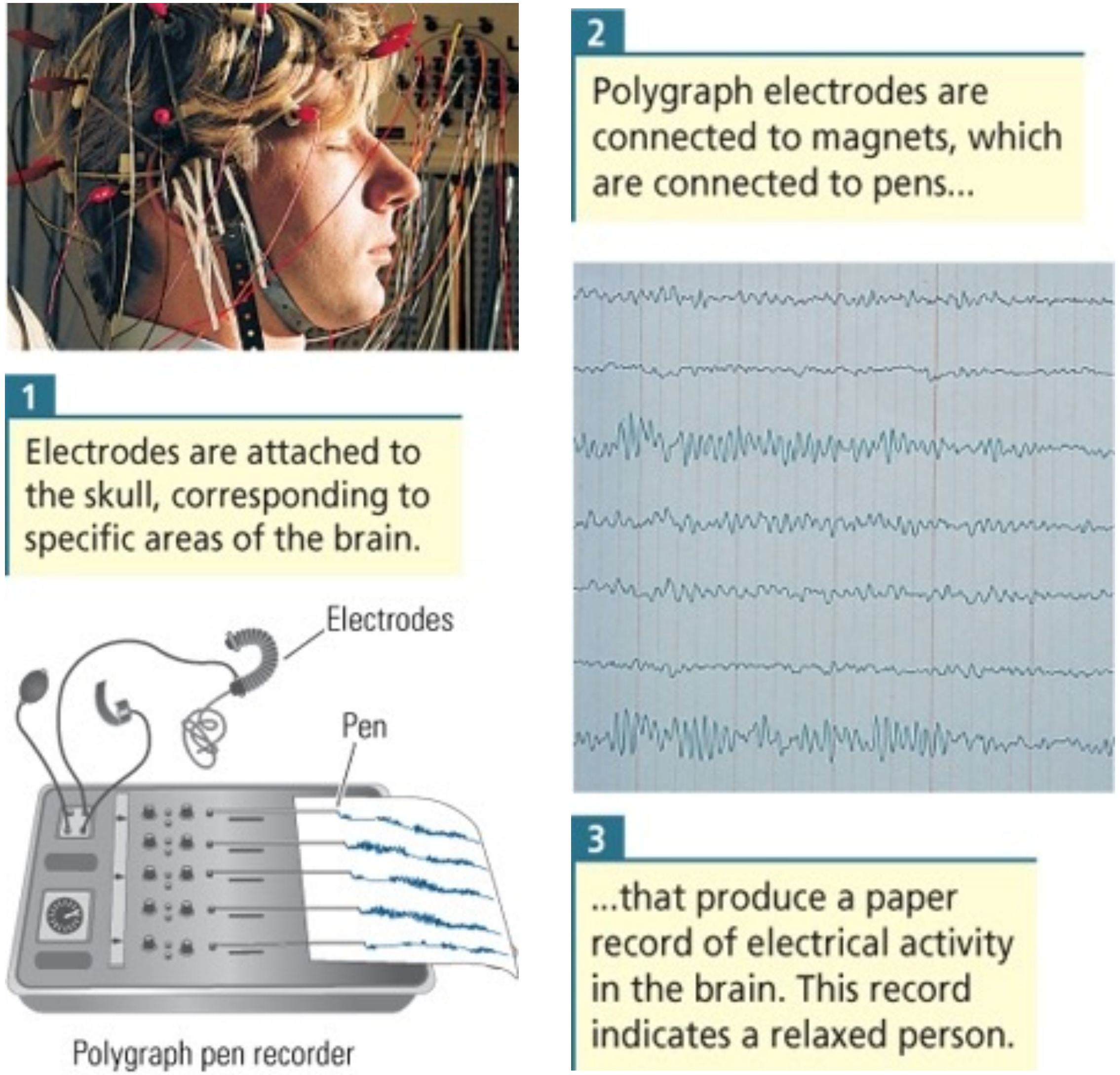
GRACE HUCKINS SCIENCE OCT 3, 2022 7:00 AM

A Huge New Data Set Pushes the Limits of Neuroscience

The Allen Institute's release includes recordings from a whopping 300,000 mouse neurons. Now the challenge is figuring out what to do with all that data.

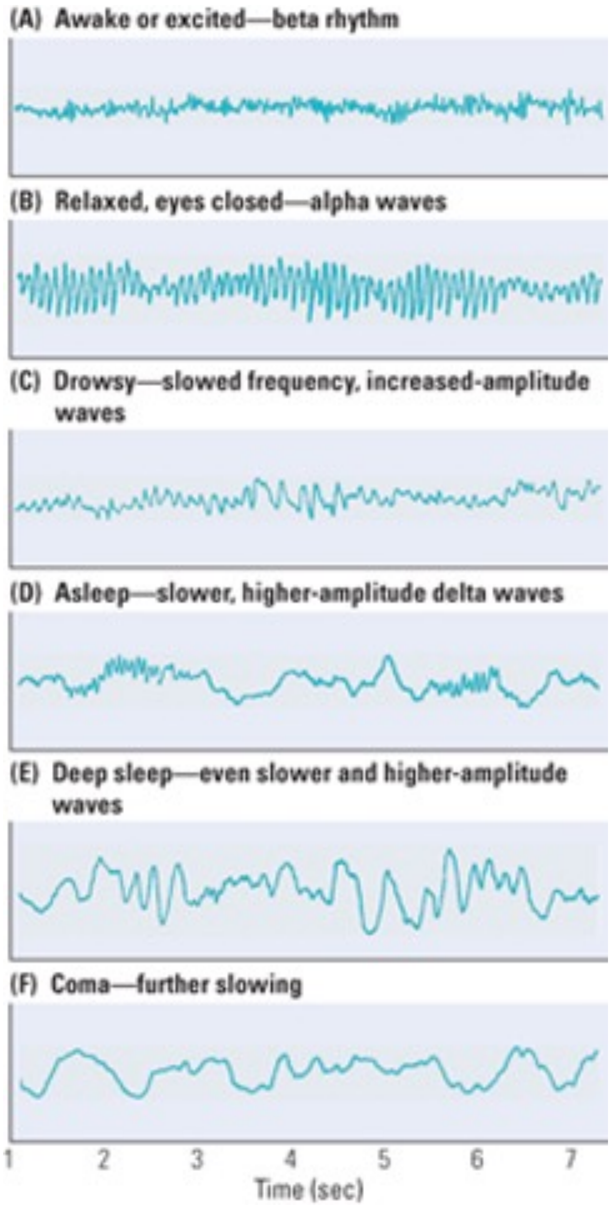


EEG

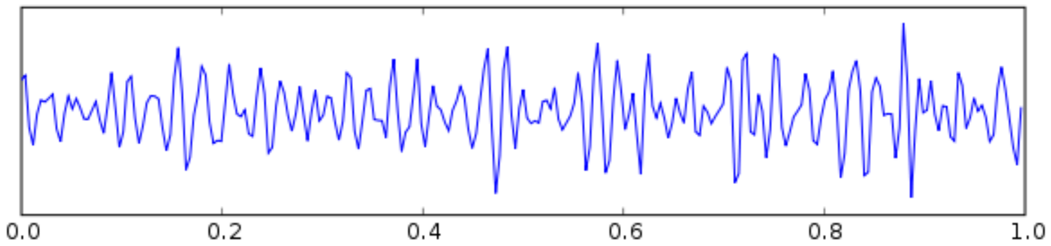


- Measuring from the scalp (limitations?)
- Waves have both a frequency and amplitude
- Frequency measured in Hz (cycles/second)

EEG waves: brain states?

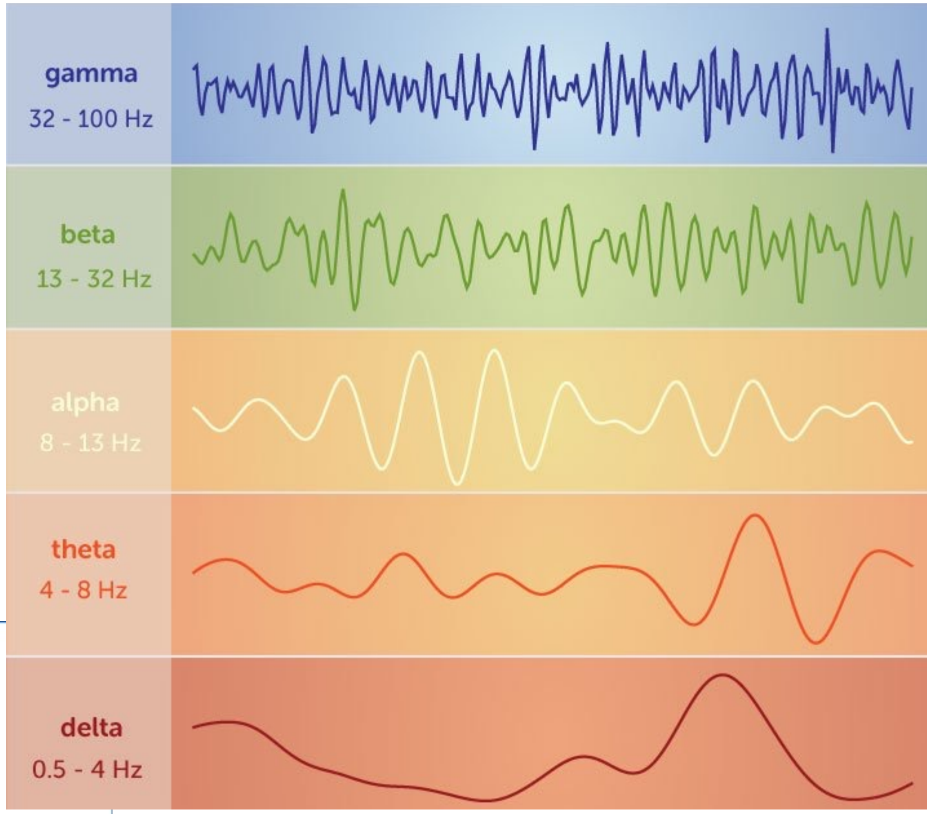


Alpha – 8-12Hz
Beta – 12-30Hz
Gamma – 26-100Hz
Delta – 0-3Hz
Theta – 4-7Hz



- Gamma waves

EEG: Sleep has multiple phases



Measured with EEG (and EMG, EOG)

Types of sleep categorized by EEG wave types!
(Frequency and amplitude)

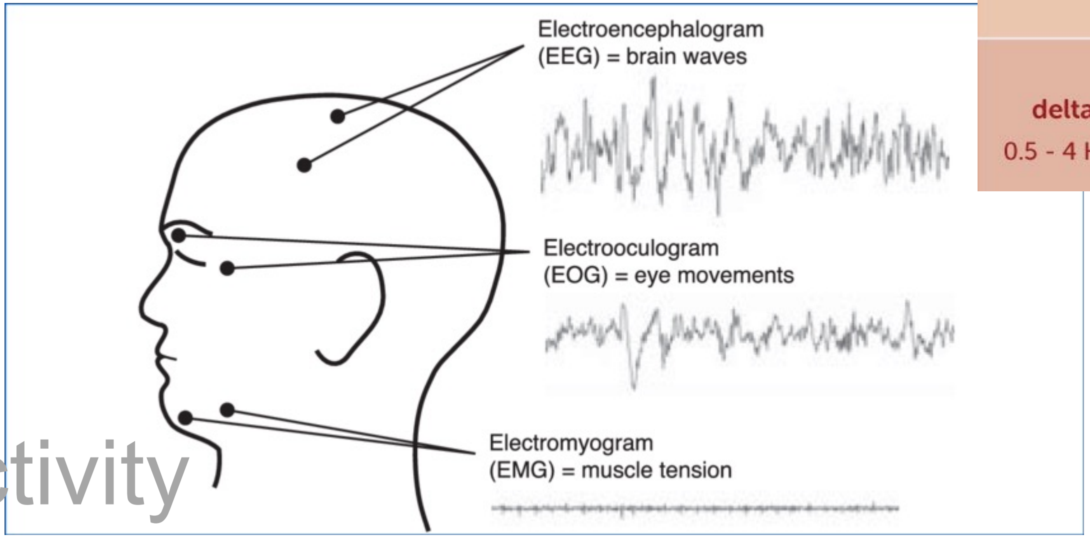
NREM 1

NREM 2

NREM 3-4

REM

Electrical activity



*NREM also known as slow-wave sleep (SWS)

But what do these waves mean?

EEG likely represents PSPs more than APs

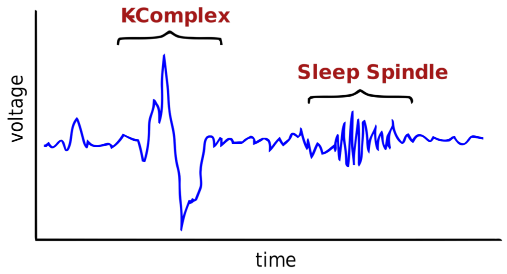
Waves show population synchrony

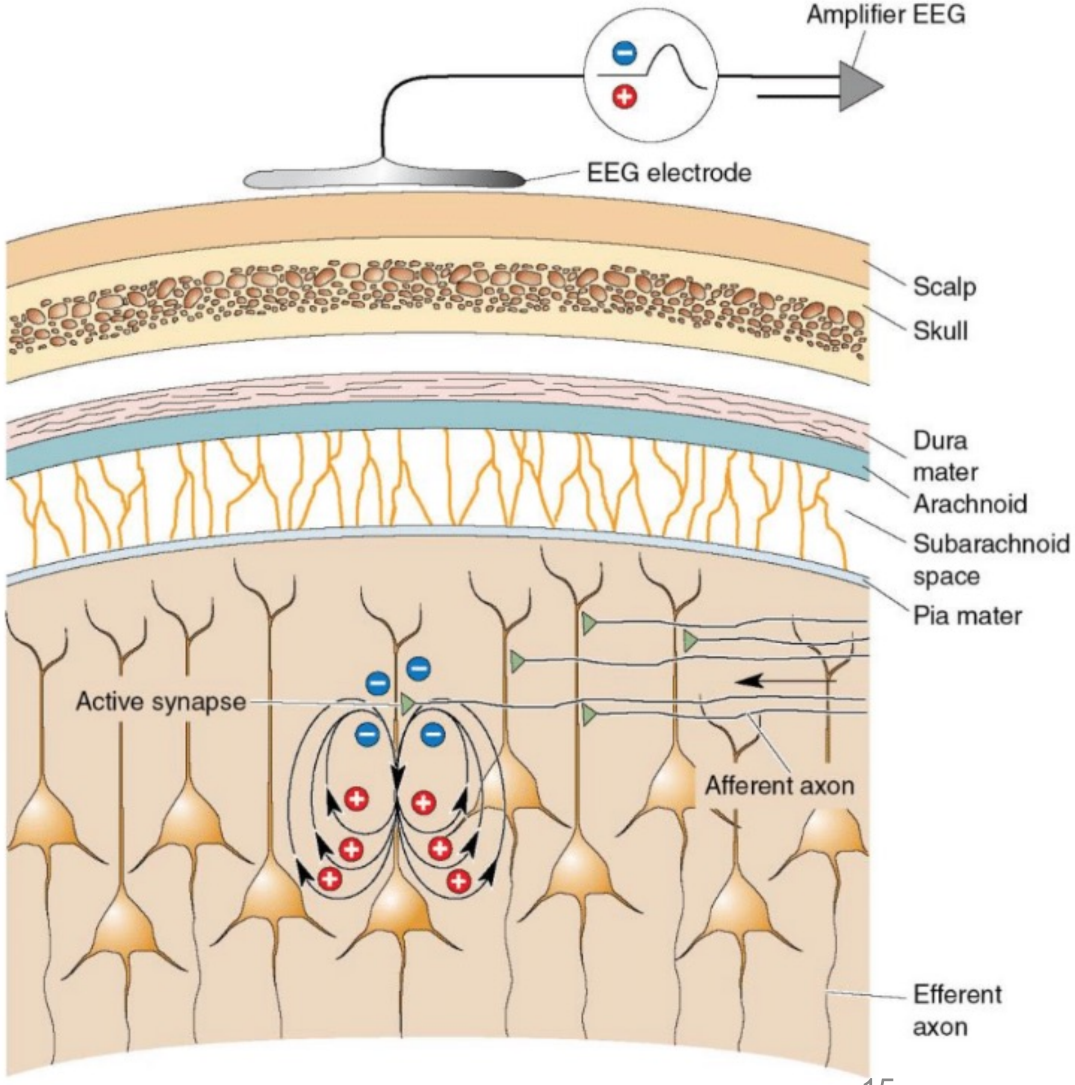
Gamma: we've discussed before

Alpha/beta: conscious brain activity?

Theta ripples: driven by medial temporal lobe?

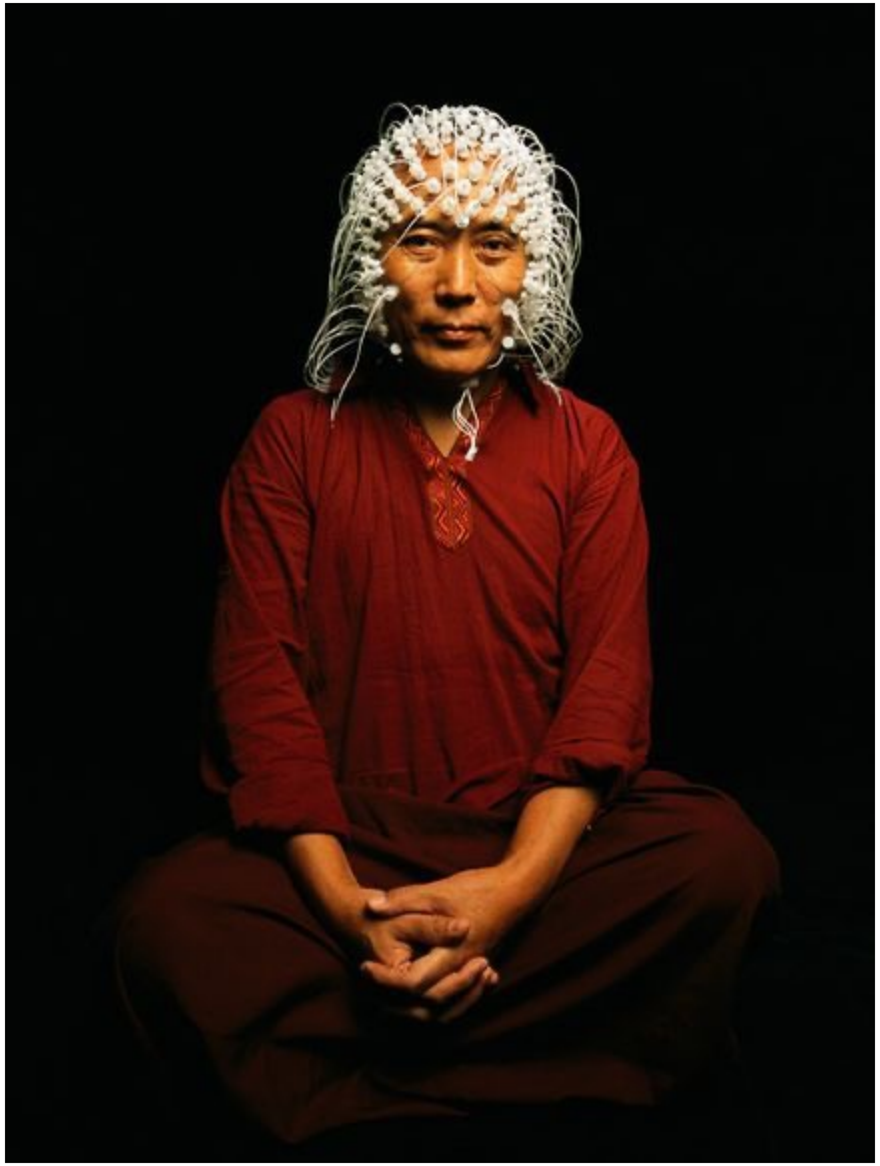
Delta: was unclear, but new ideas
related to sleep



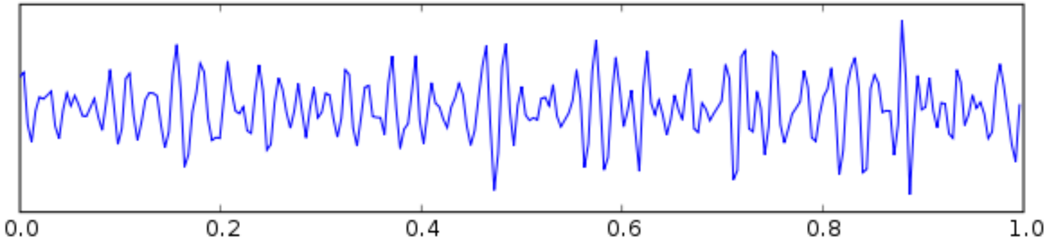


Electrical activity

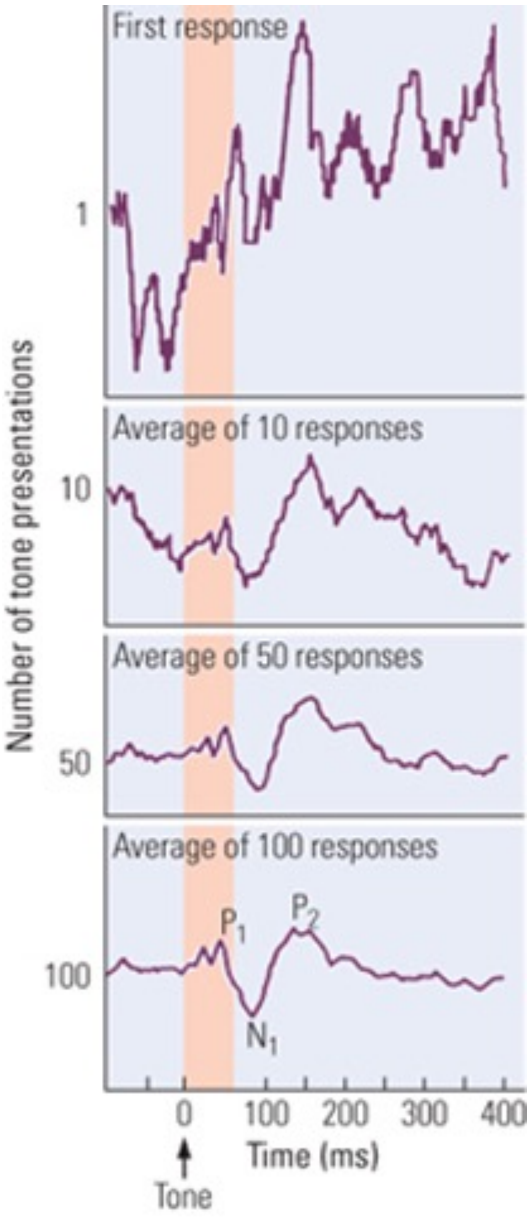
EEG: gamma waves

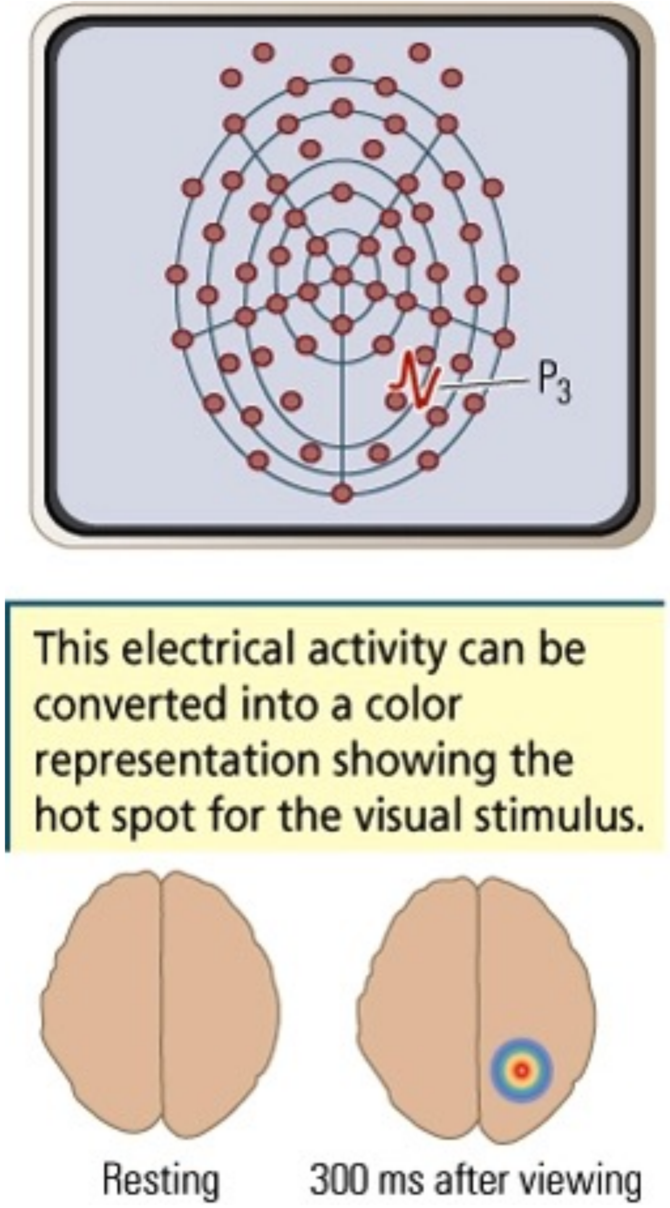


- “Information processing”, attention, maybe consciousness
- Meditation: highest amplitude gamma recorded (Lutz *et al.* 2004)
  - Gamma changes with skill level!
- Rhythm possibly mediated by fast-spiking, GABAergic interneurons (Cardin *et al.* 2009)



ERPs

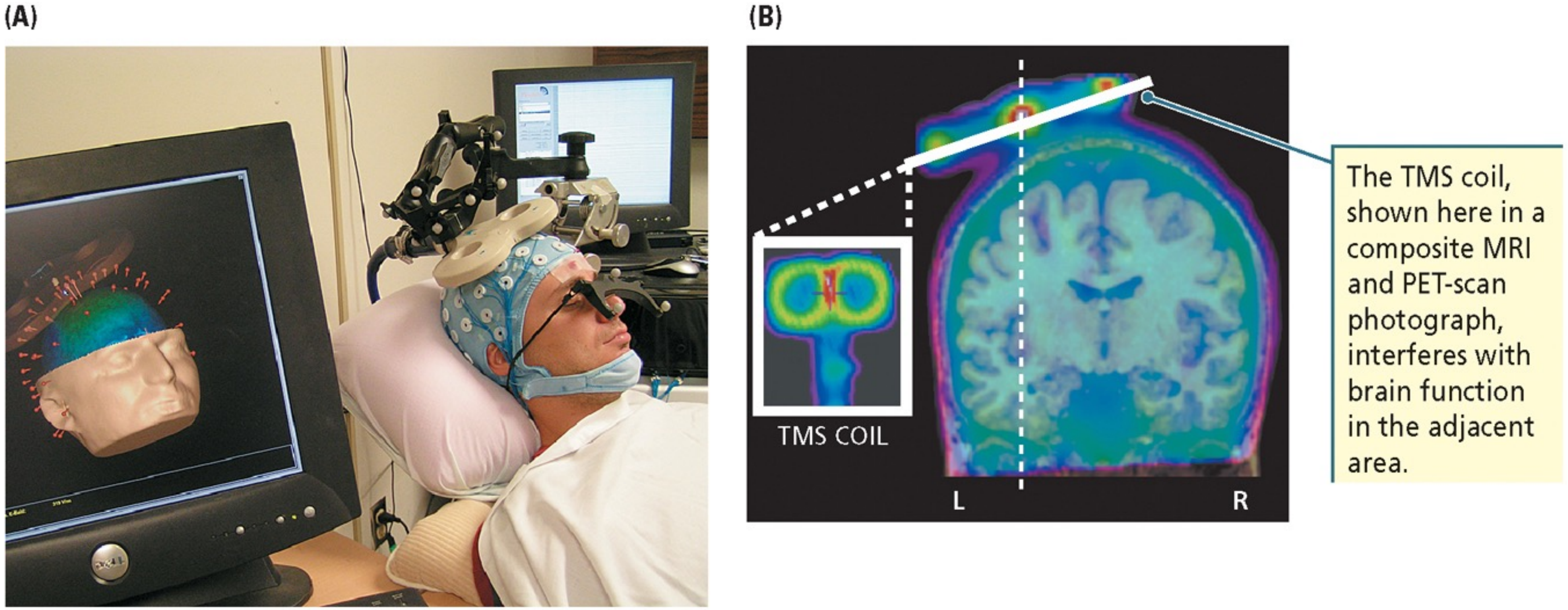




- Averaged response to a stimulus
- Subcomponents

Electrical activity

Transcranial magnetic stimulation



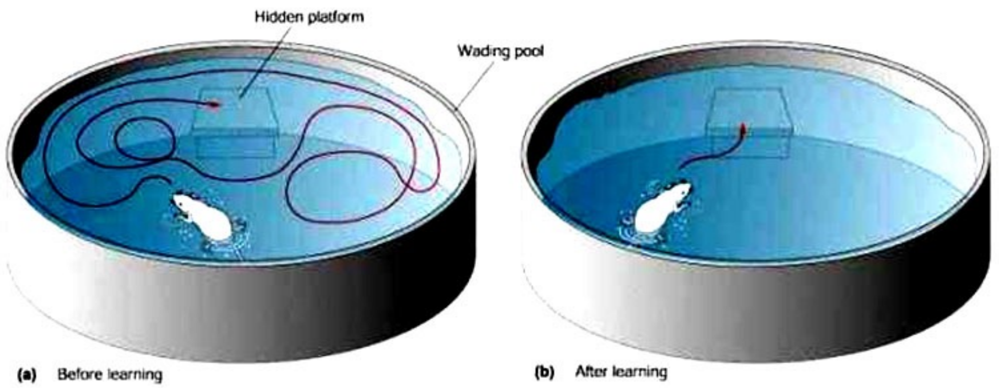
A: Marcello Massimini/University of Milan. B: Composite MRI and PET scan from Tomas Paus, Montreal Neurological Institute.

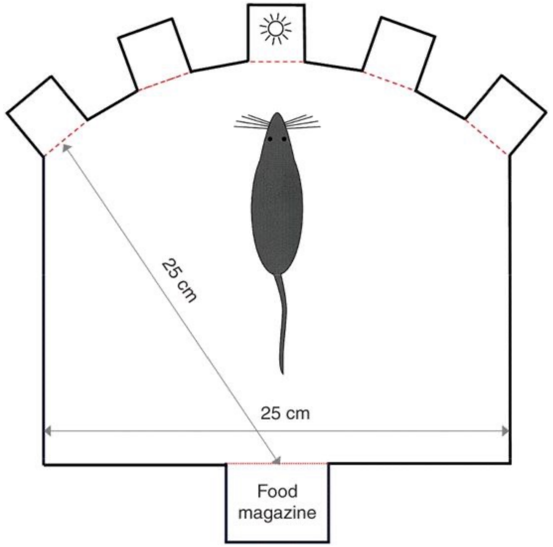
- Usually to make “virtual lesions”
- Potential therapeutic applications
- https://www.youtube.com/watch?v=FMR_T0mM7Pc

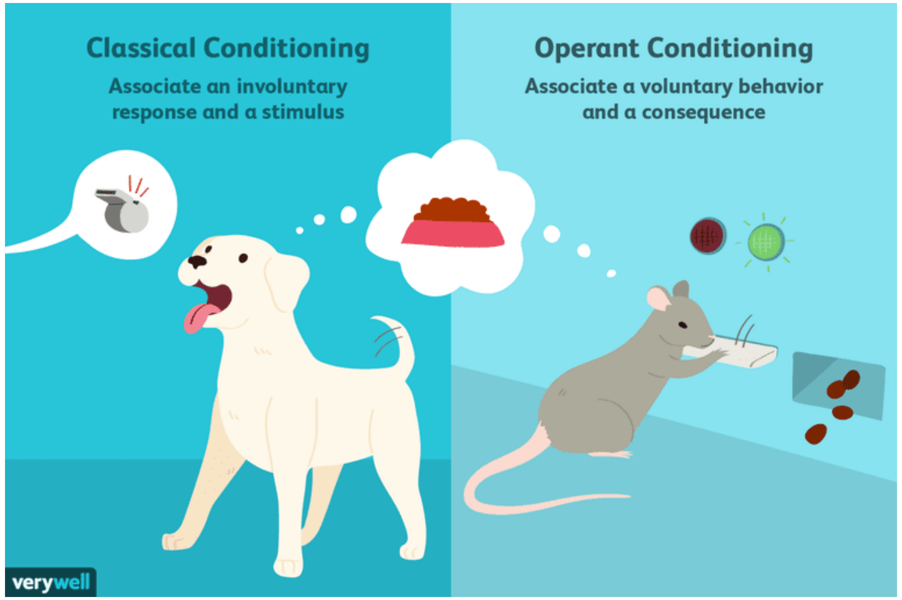
Deep thoughts by the rat

Some examples:

- Morris water maze
- 5-choice serial reaction time task
- Conditioning (classical, operant)
- T-maze







BUT the quality of your model is determined by the quality of your behavioural assay

A notable offender:
the forced-swim test (FST)

FST used to measure depression in the rodent, as well as antidepressant medication efficacy

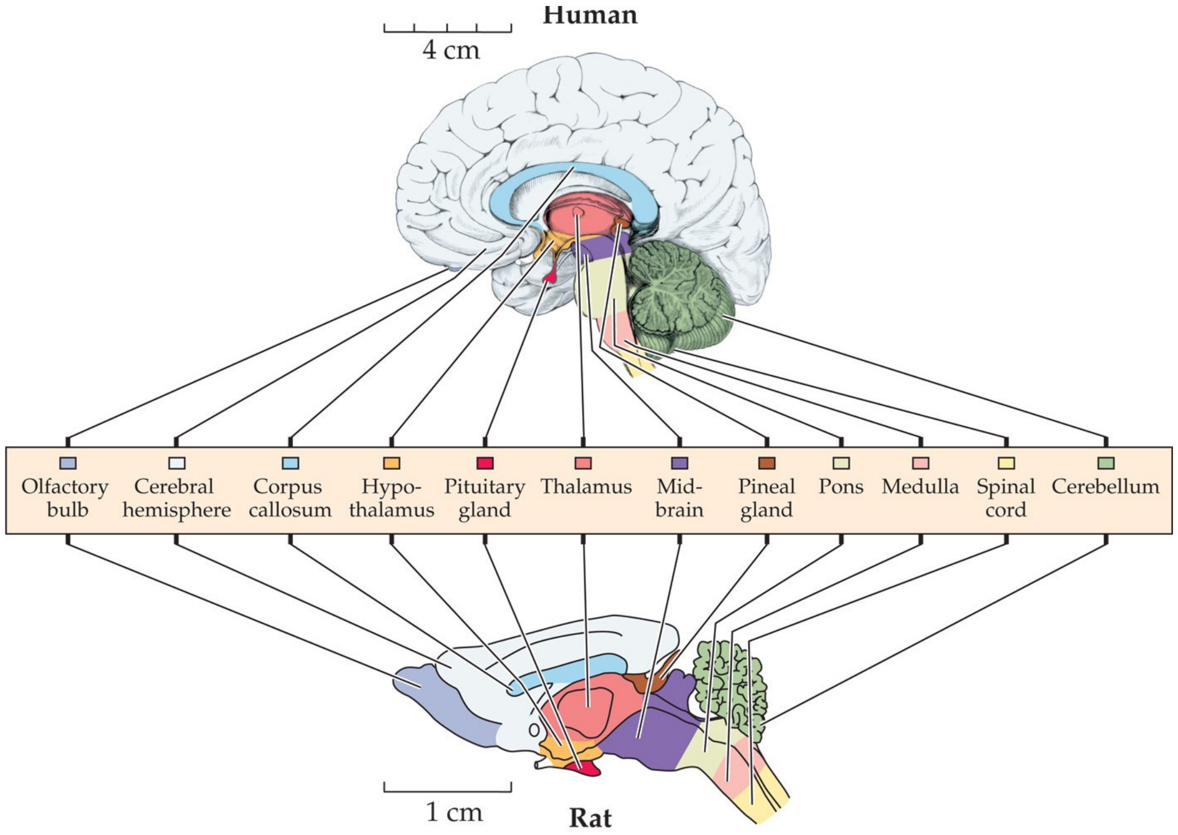
Difficulties in interpretation?

Why use animal models?

Because they truly *model*

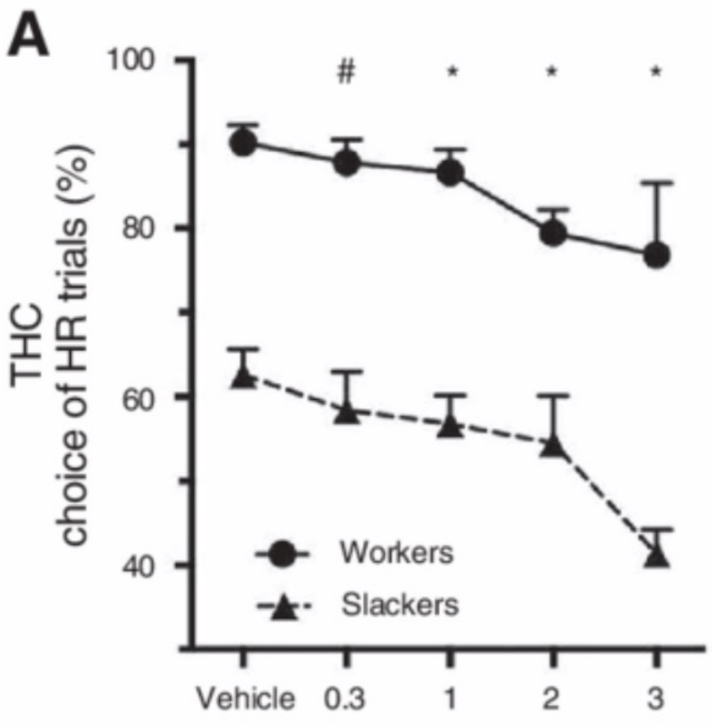
Mammalian brain similarity

Animal cognition is sophisticated



https://www.youtube.com/watch?v=RRRISM23ABk

Drug “Challenge”

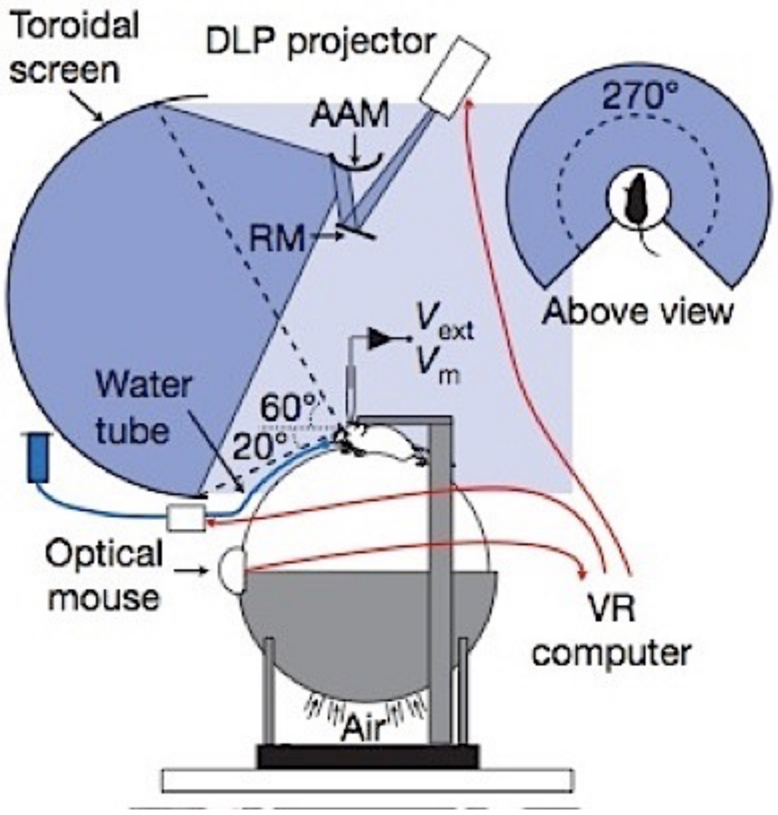


- Potential Routes
  - Intramuscular (IM)
  - Intravenous (IV)
  - Subcutaneous (SC)
  - Intraperitoneal (IP)
    - Perhaps most common
  - Intraventricular
    - Overcomes problems with drugs passing the blood-brain barrier

  - Multiple doses is best (e.g. saline only, then low, med, high)
    - Within-subjects design

Invasive Electrical Recording Methods

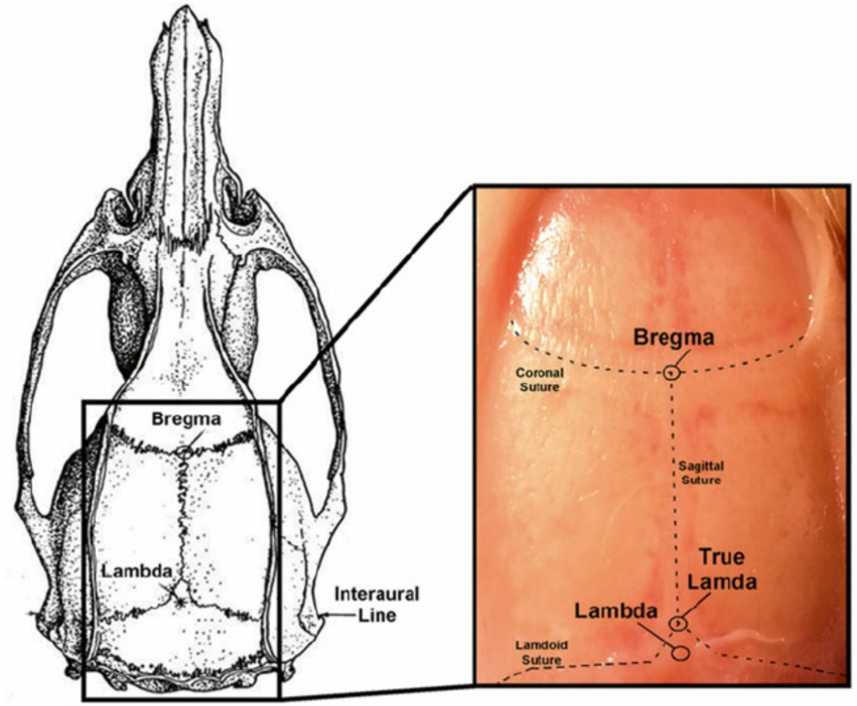
- Four Invasive Electrophysiological Recording Methods
  - – Intracellular Unit Recording
  - – Extracellular Unit Recording
  - – Multiple-Unit Recording
  - – Invasive EEG Recording

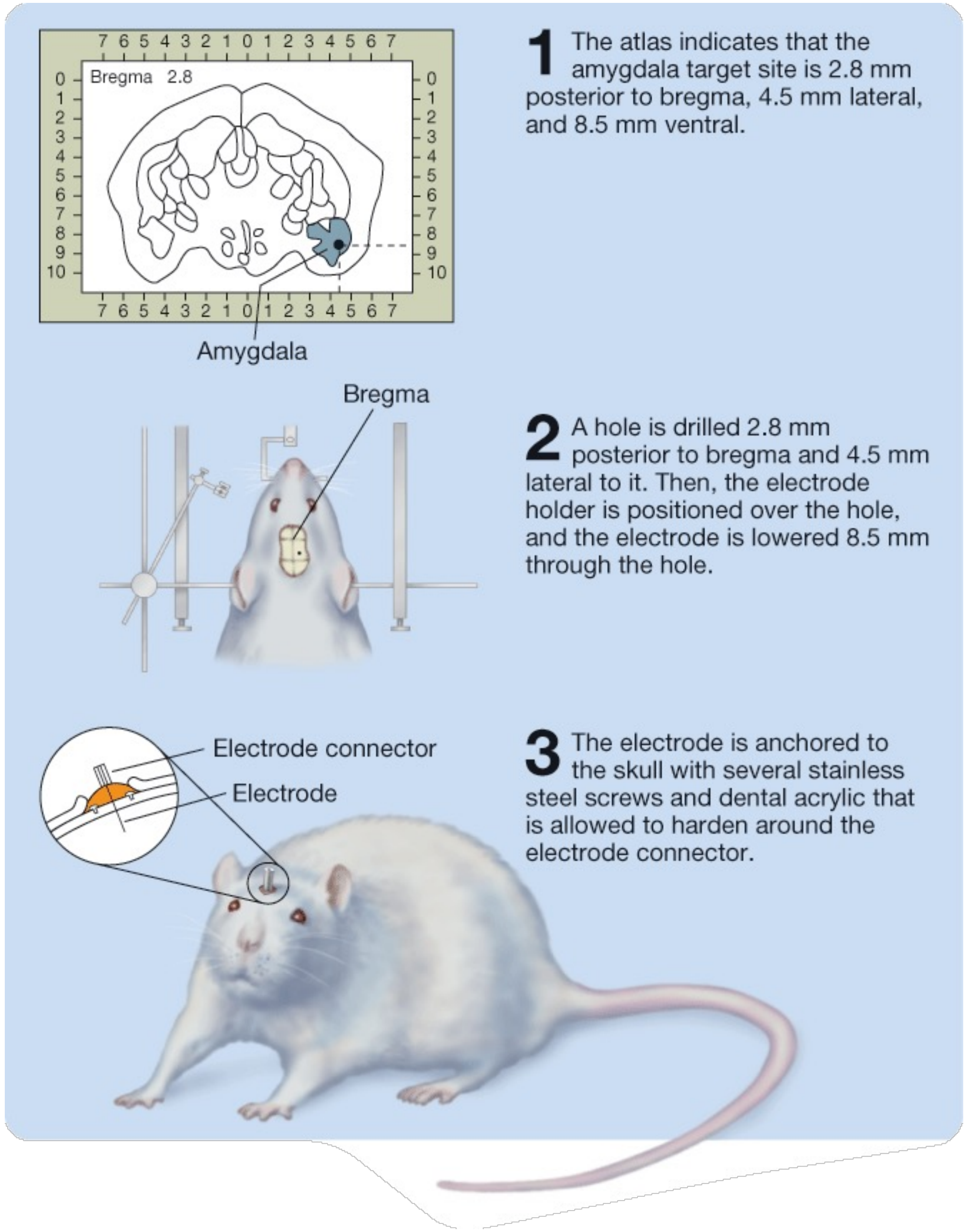


https://www.youtube.com/watch?v=1DJOTEDBA2c

Stereotaxic surgery

- For lesions, optogenetics, electrodes, more
- Employs stereotaxic atlas and instrument
- Allows accurate placement of lesions, probes, electrodes, etc.
- Reference point used is bregma

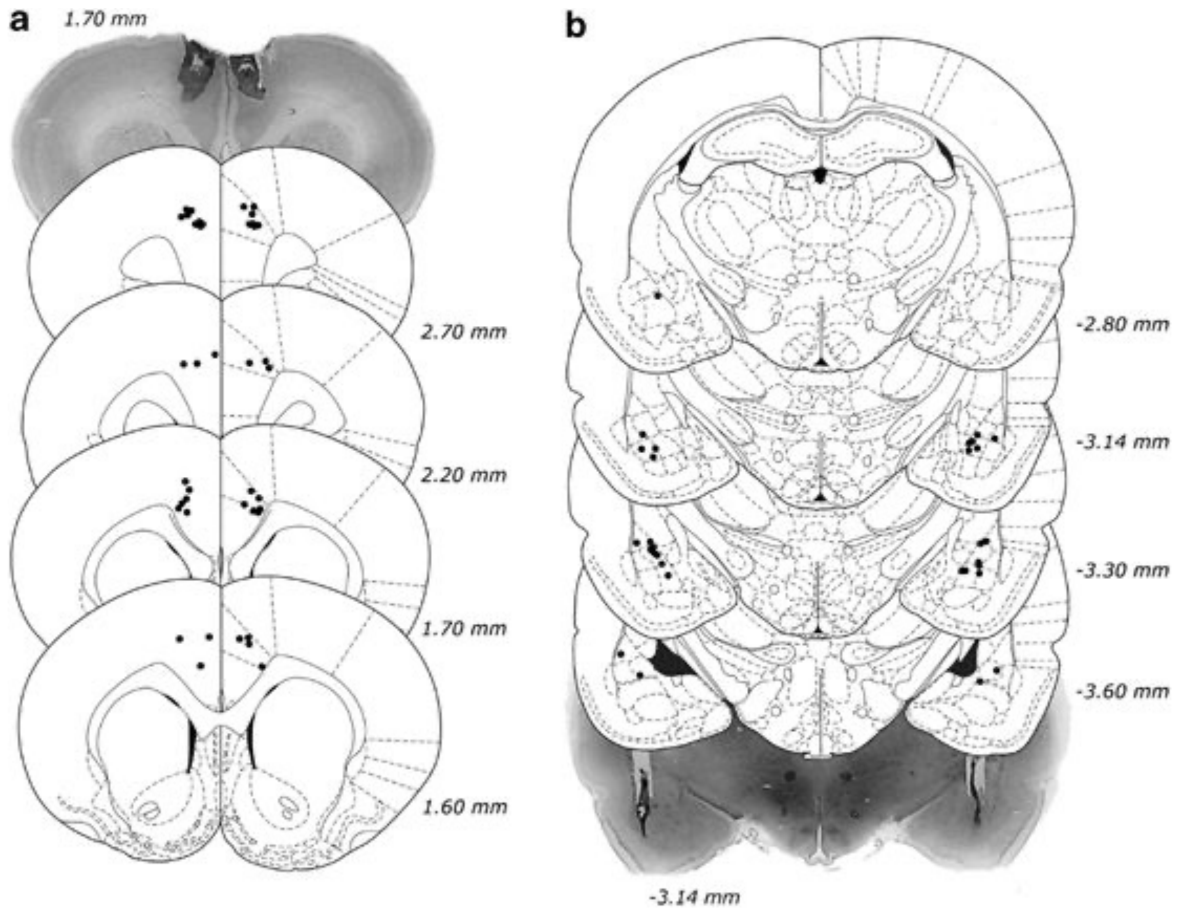




Lesion methods

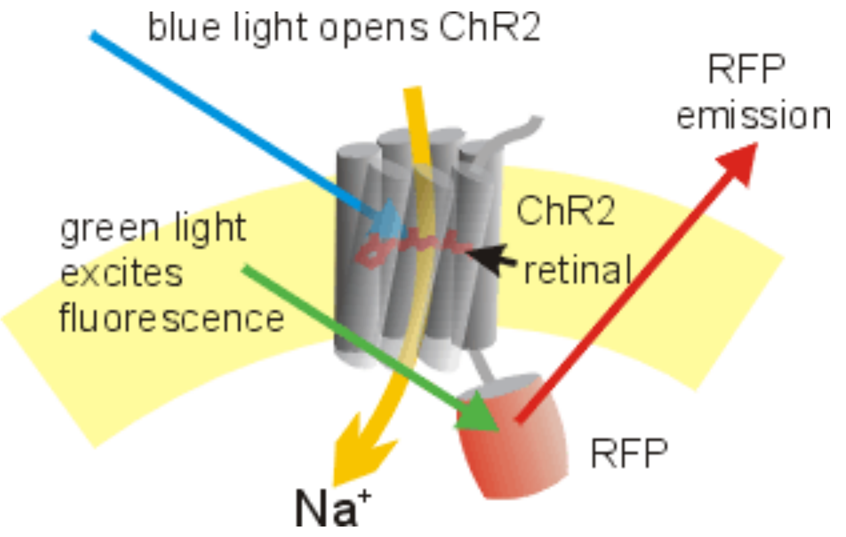
- Chemical, i.e. excitotoxic lesions
  - e.g. quinolinic acid, ibotenic acid
- Selective chemical lesions
  - e.g. 6-hydroxydopamine (6-OHDA), 5,7-dihydroxytriptamine (5,7-DHT)
- Reversible lesions, aka inactivations
  - Cannulae
  - e.g. baclofen + muscimol
  - Benefit: within-subjects design!

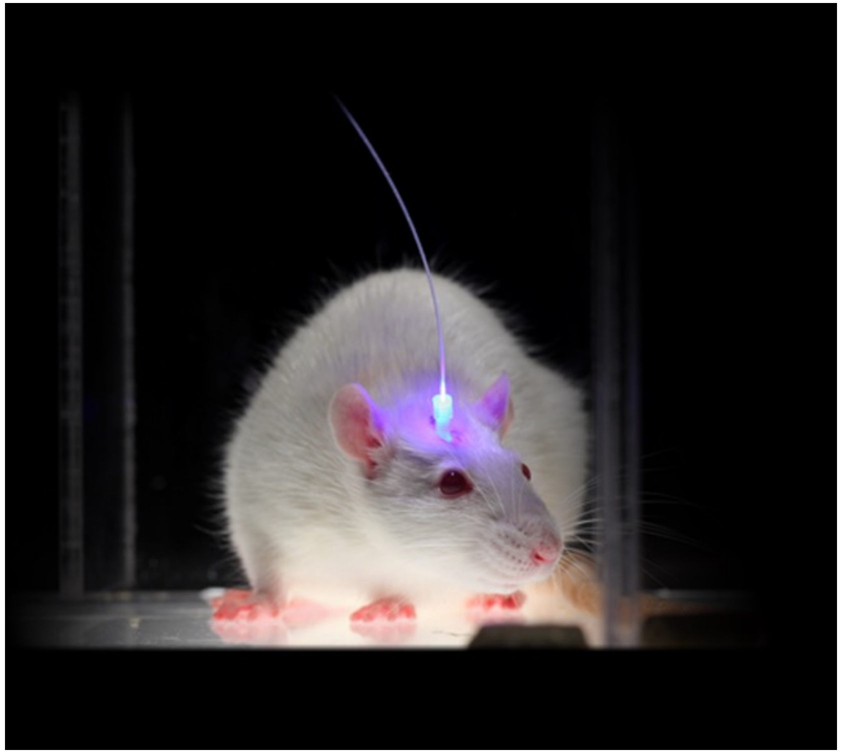
- Interpretation of lesion studies
- Ideal post-surgery testing window?
- Unilateral vs. bilateral vs. contralateral lesions



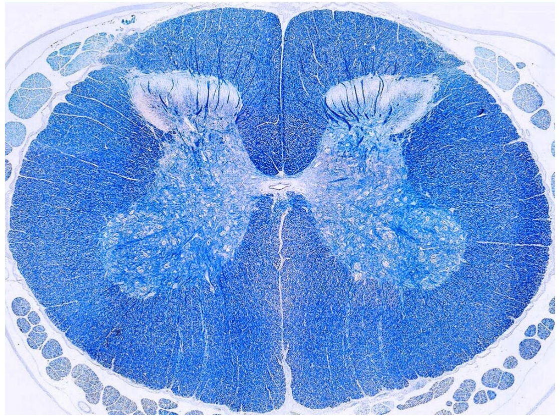
Optogenetics

- Introducing: light-gated ion channels!
  - Channelrhodopsins
- Use system-specific transcription factors
- Can be used for both recording/mapping and manipulation





Reminder: stains are cool



LFB stain

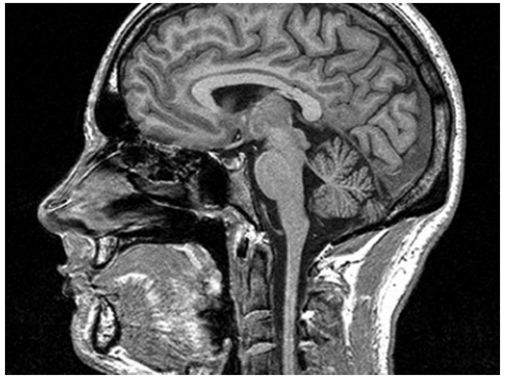
- Golgi stain
- Nissl stain / cresyl violet stain
- Fibre stains
  - Luxol-fast blue (LFB)
  - Toluidine blue
- Green fluorescent protein (GFP)
  - Many derivatives (e.g. YFP, BFP)
  - Can be inserted into living cells!
    - e.g. Single-neuron electroporation
- And much more!

Courtesy Dr. Kurt Haas

Tectum neuron with GFP in awake animal!

Neuroimaging: structural and functional

- Static: AKA structural
  - Computerized axial tomography (CAT / CT)
  - Magnetic resonance imaging (MRI)
  - Diffusion tensor imaging (DTI)



- Dynamic: AKA functional
  - Positron emission tomography (PET)
  - Functional MRI (fMRI)
  - Resting-state functional connectivity MRI (rsfcMRI)

X-Ray

X-ray tube, X-ray beam, film (or detectors)

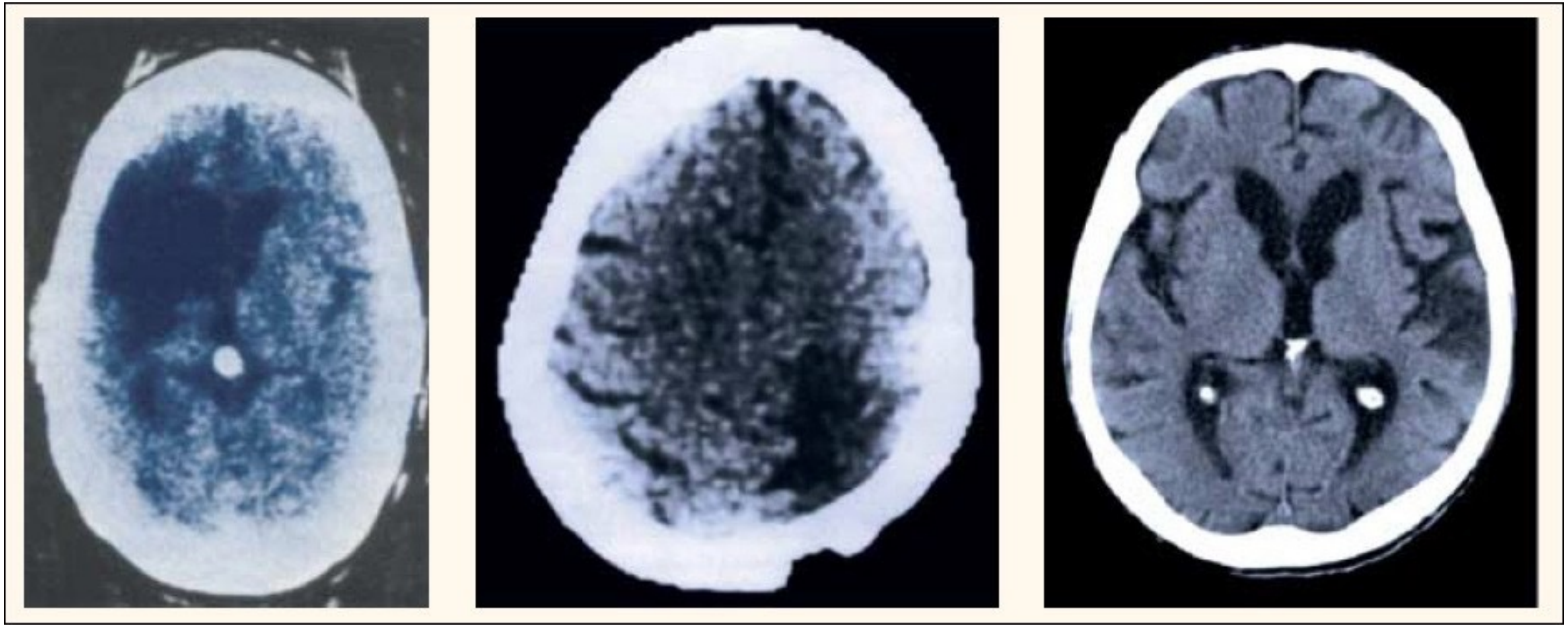
What can be seen?

Computed tomography (CT)

The tube and detector

Computed tomography (CT)

Rorden & Karnath, 2004



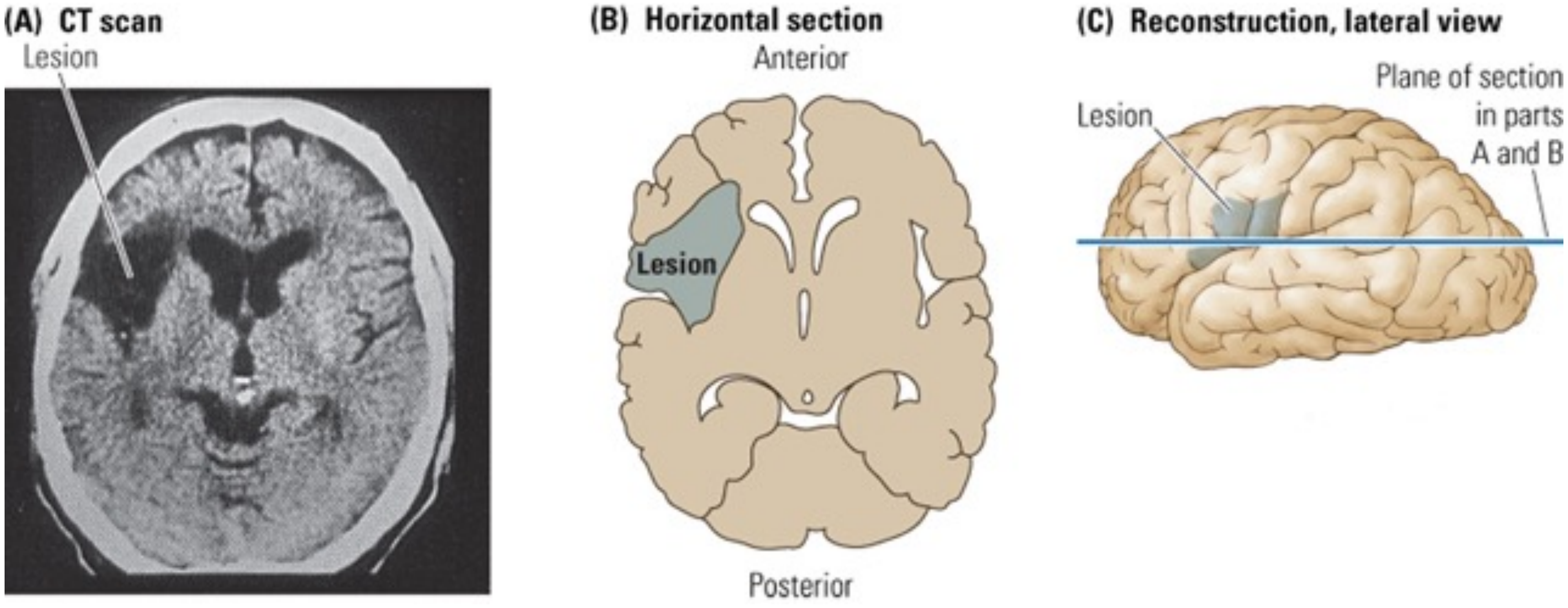
1977 1983 2004

Only as good as its algorithms

Useful for?

Drawbacks?

Computed Tomography (CT)

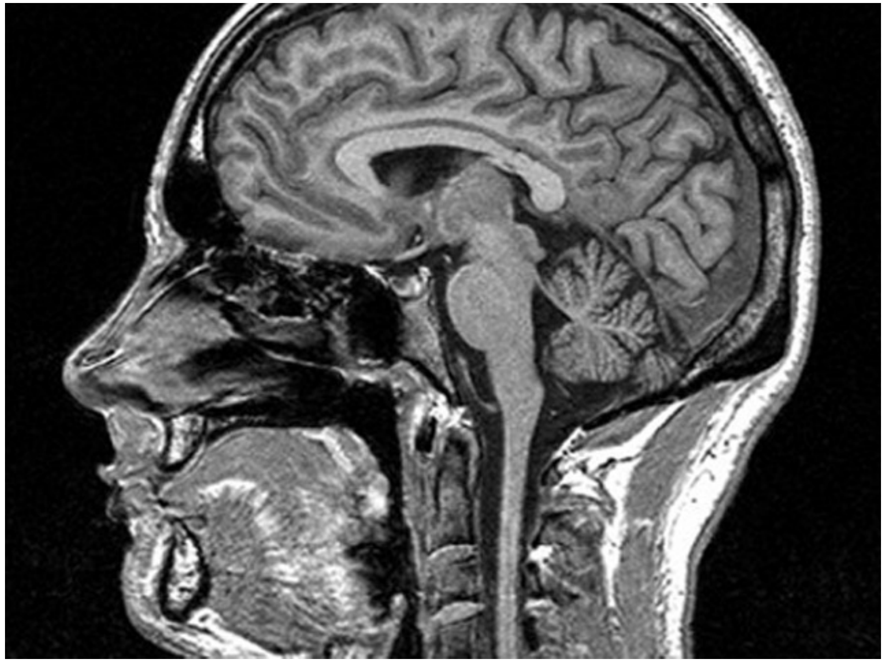


- Previously useful for stroke
  - Why?

Structural imaging

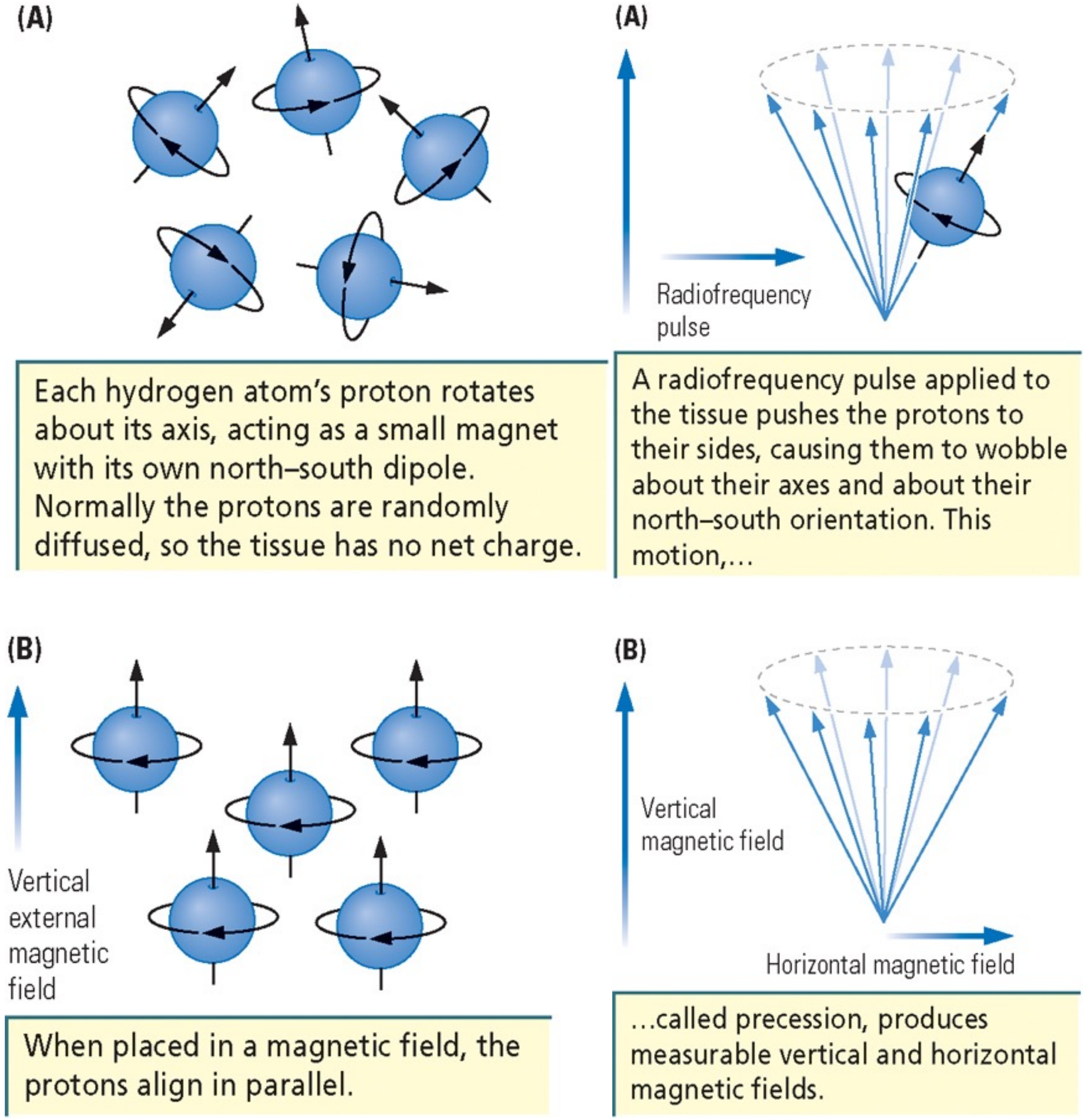
Magnetic resonance imaging (MRI)

https://www.youtube.com/watch?v=6BBx8BwLhqg

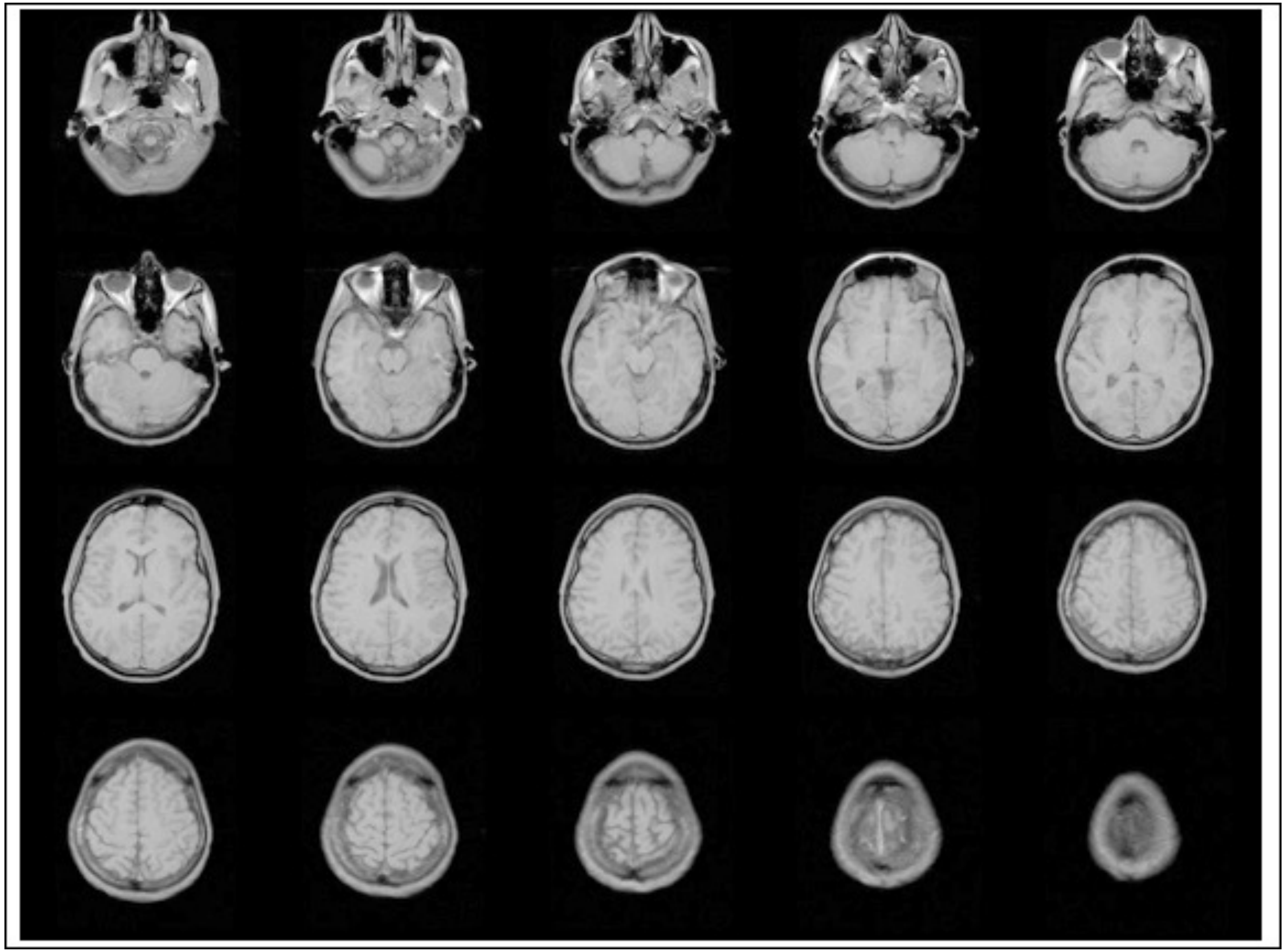


Structural imaging

MRI

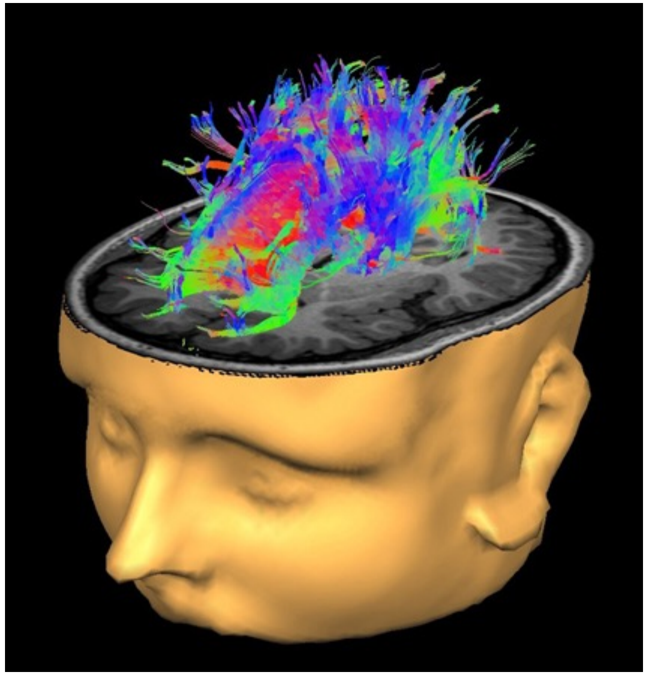

(A)
Each hydrogen atom's proton rotates about its axis, acting as a small magnet with its own north–south dipole. Normally the protons are randomly diffused, so the tissue has no net charge.
(B)
Vertical external magnetic field
When placed in a magnetic field, the protons align in parallel.
(A)
Radiofrequency pulse
A radiofrequency pulse applied to the tissue pushes the protons to their sides, causing them to wobble about their axes and about their north–south orientation. This motion,…
(B)
Vertical magnetic field
Horizontal magnetic field
…called precession, produces measurable vertical and horizontal magnetic fields.

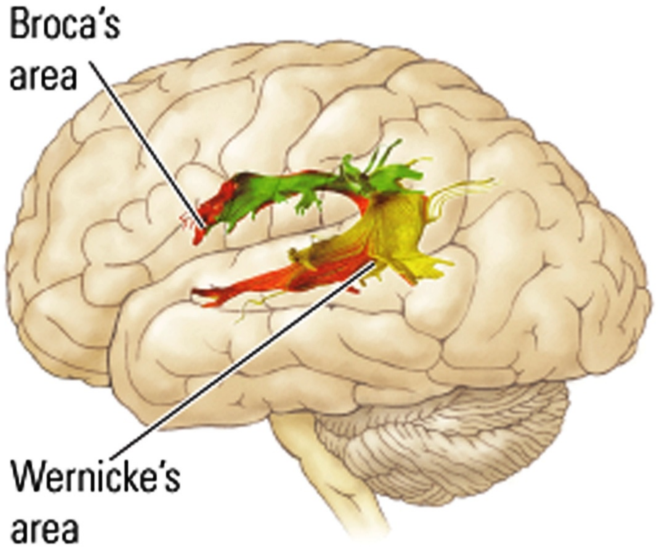
MRI

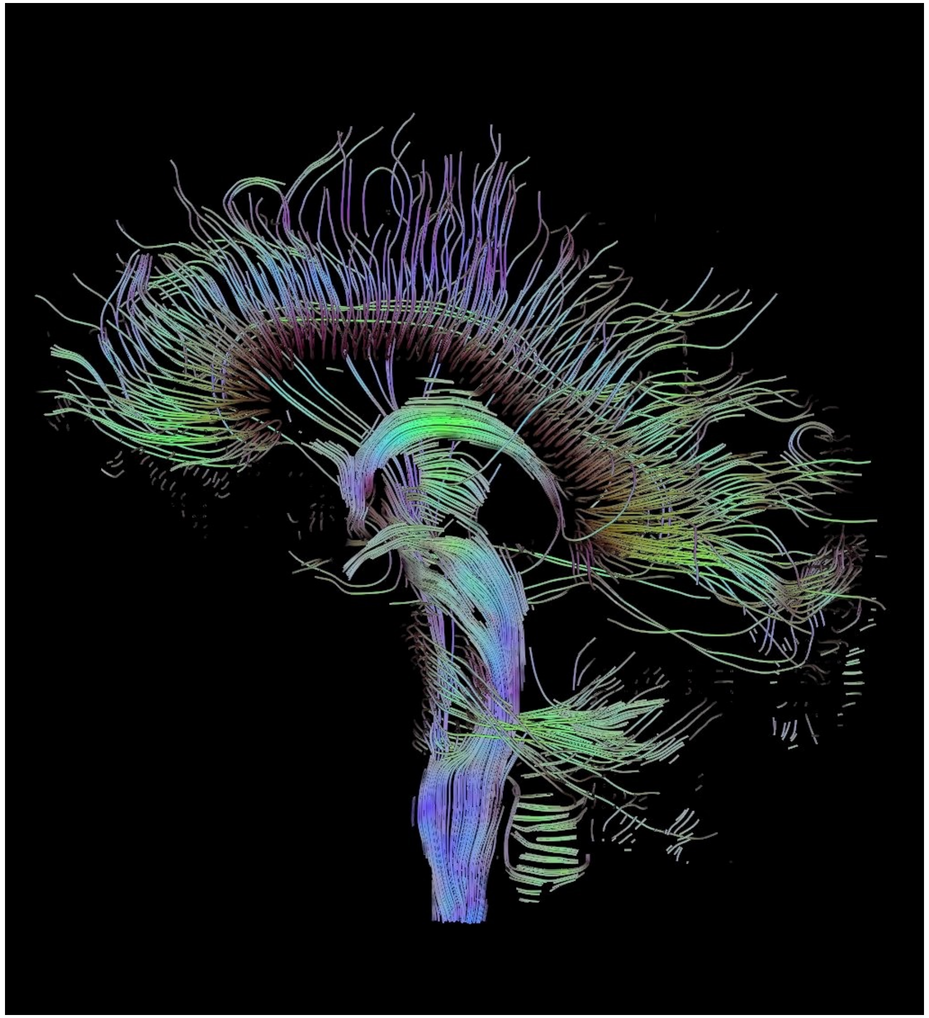


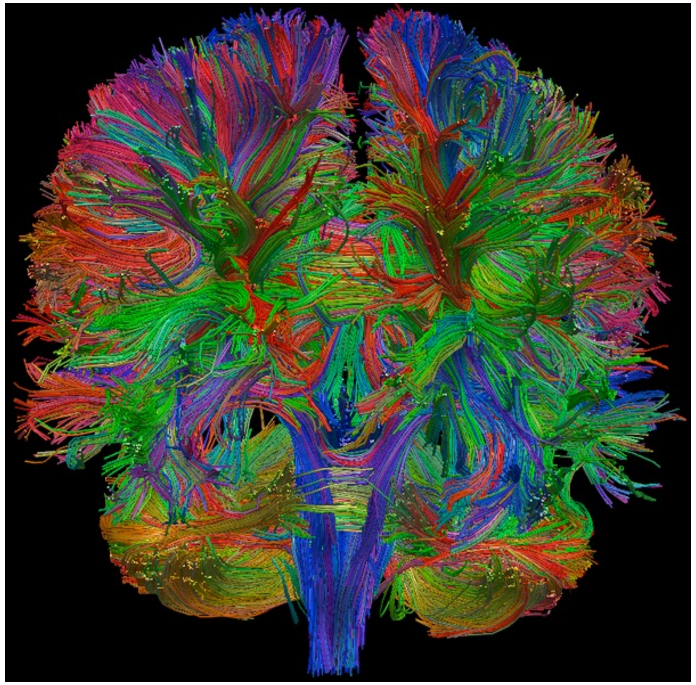
Structural imaging

Diffusion Tensor Imaging (DTI)



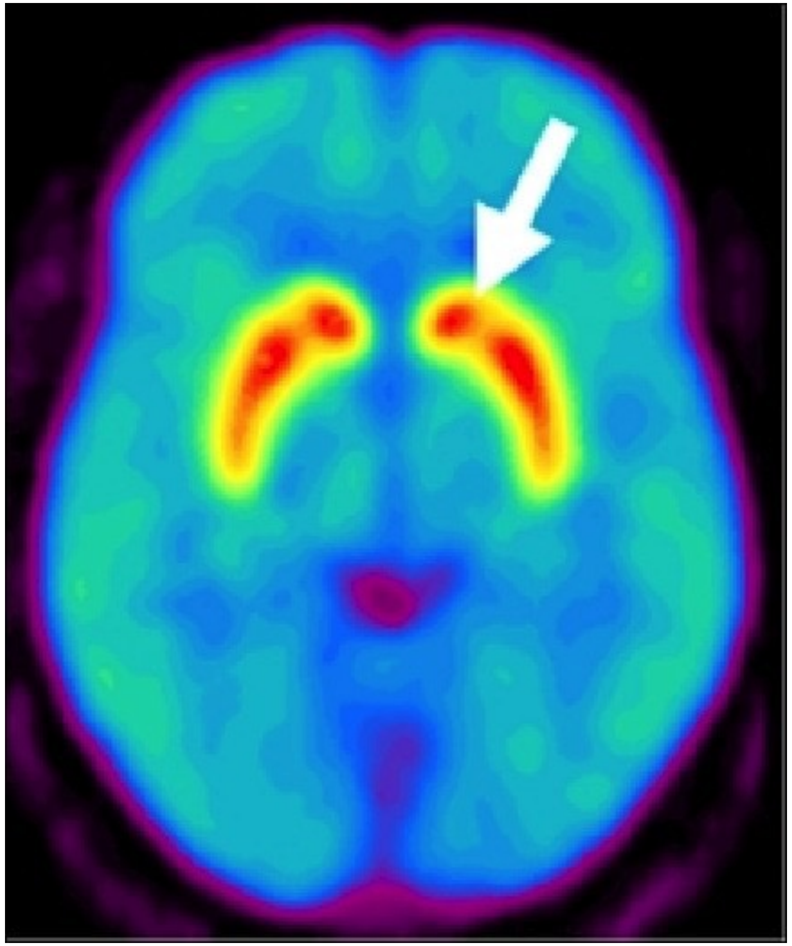






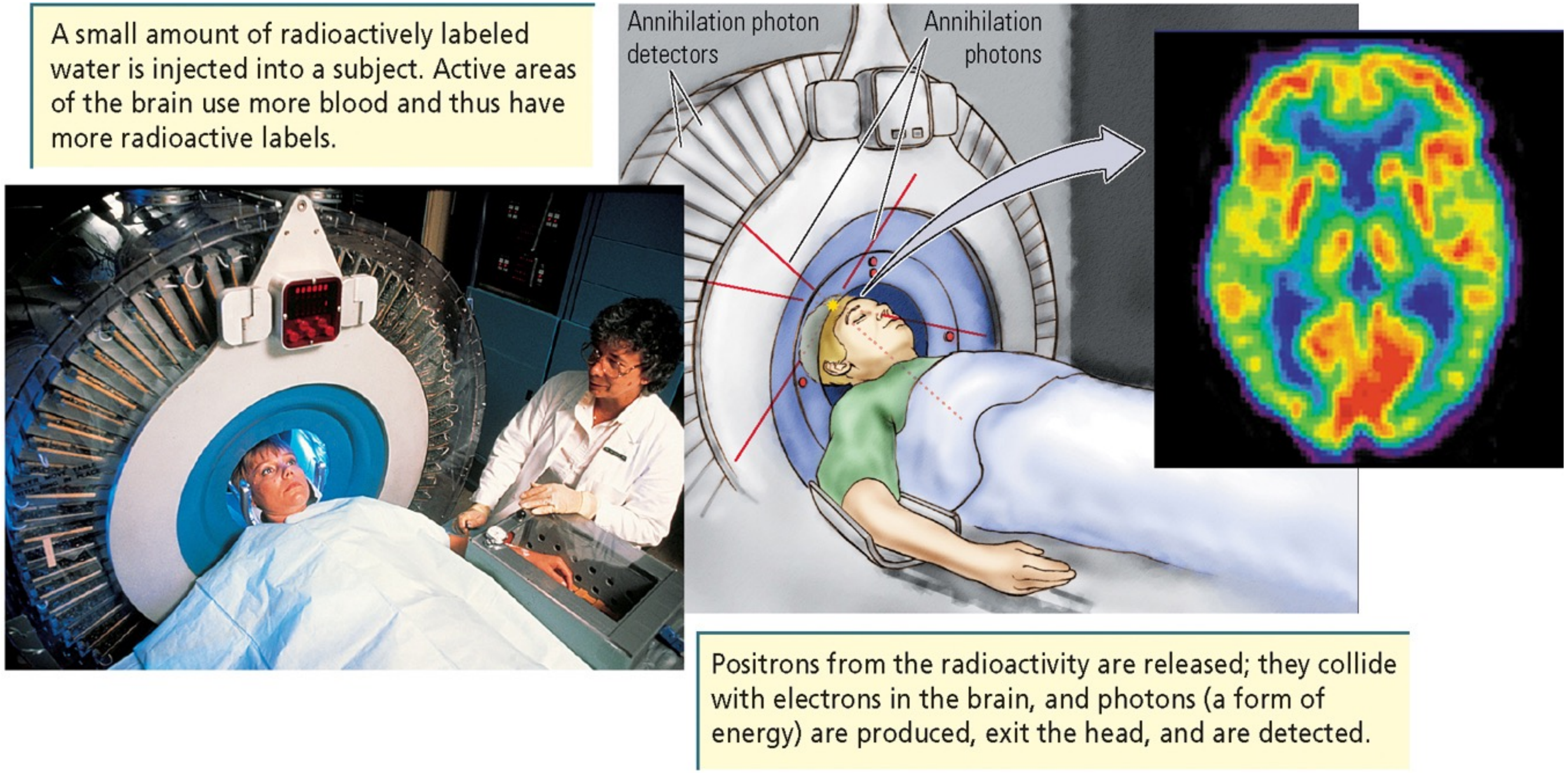
- Variant of MRI
- Relies on how water molecules move in brain
- Useful for?

Positron Emission Tomography (PET)



PET using radiolabelled cocaine (from Shumay et al., 2011)

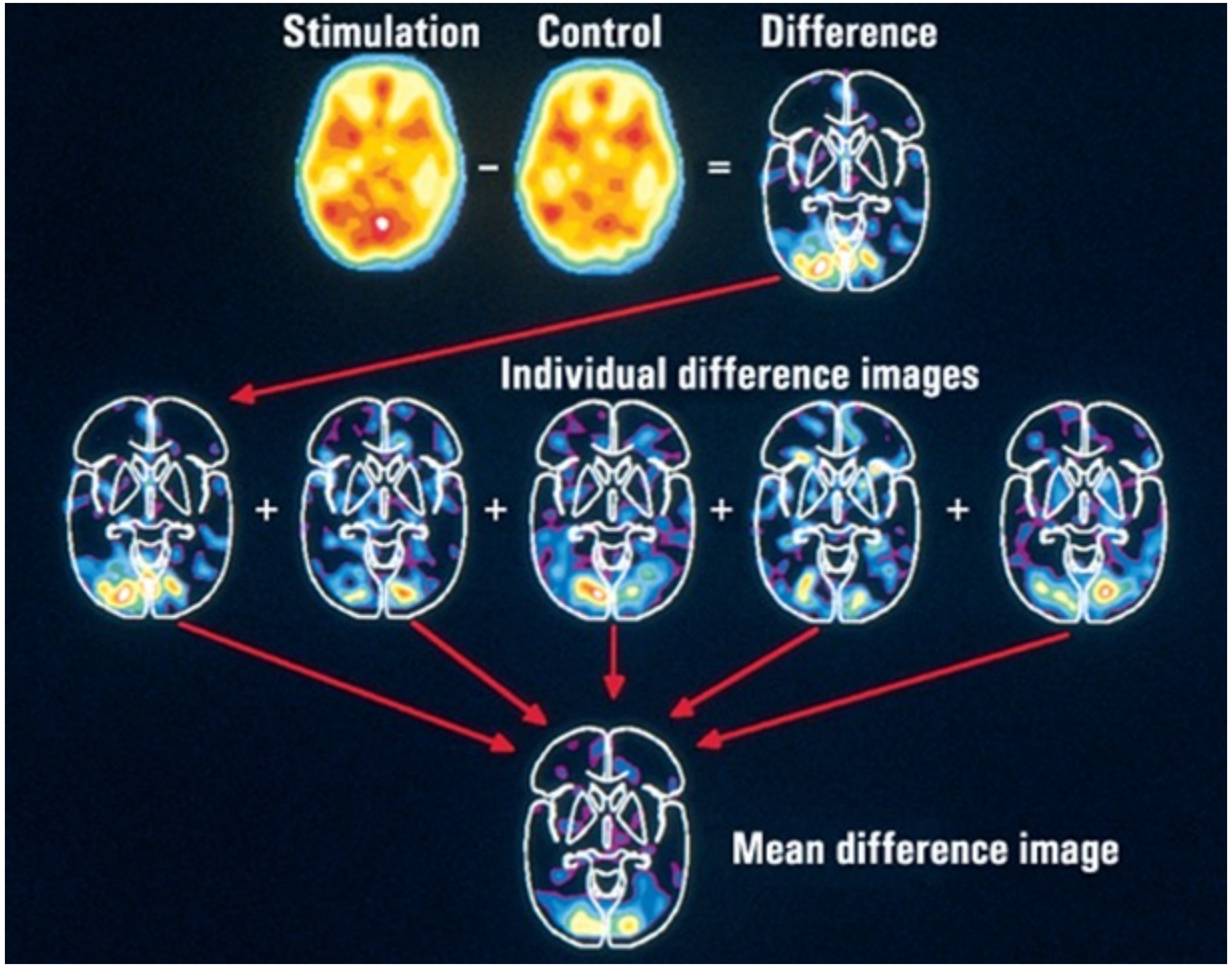
PET



PET scanner from Hank Morgan/Science Source; PET scan from Science Source.

- Indirect measure (as is fMRI)
  - Meaning? Potential issues?

PET



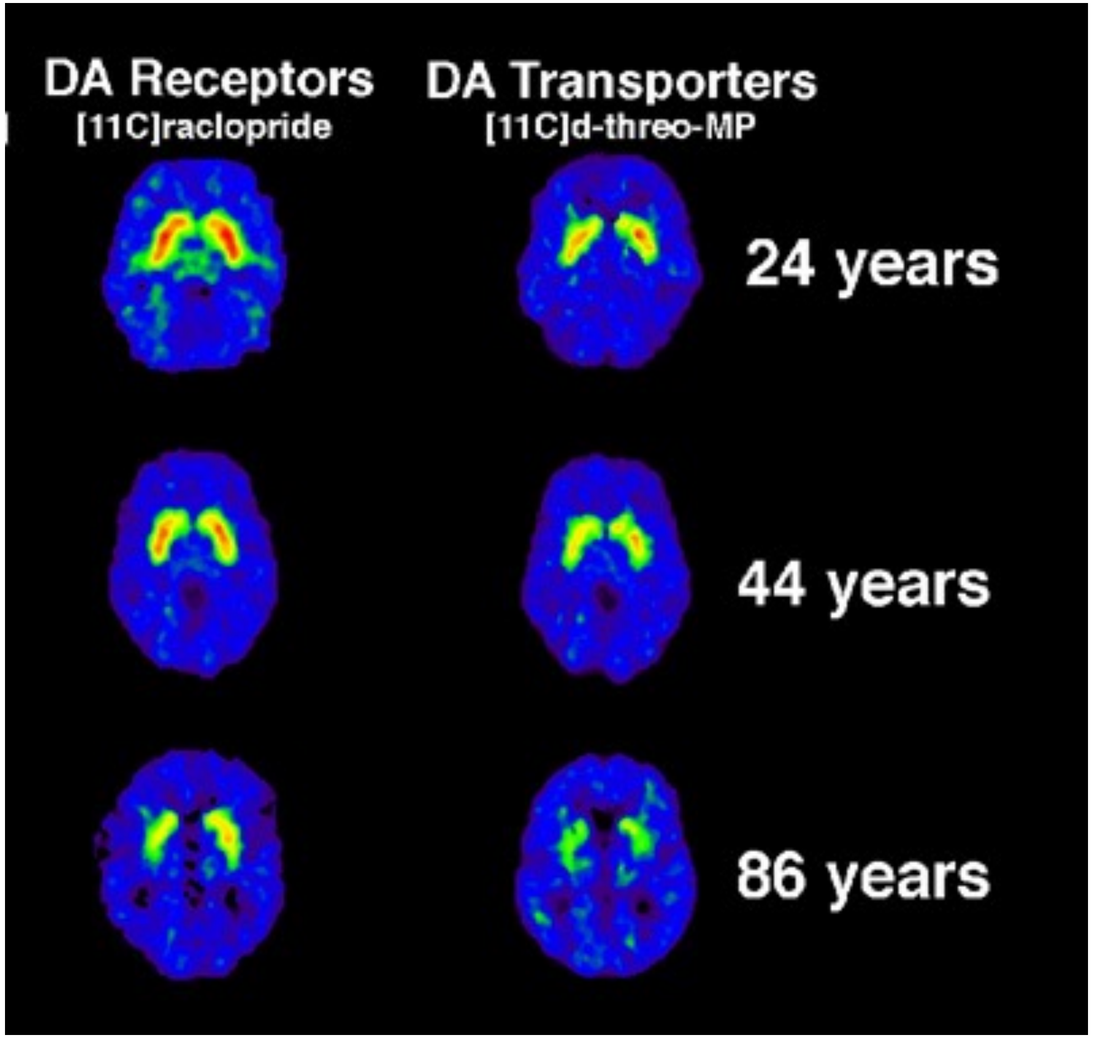
- Subtraction method (similar for some fMRI)
  - Potential issues?

PET: less common now, but…

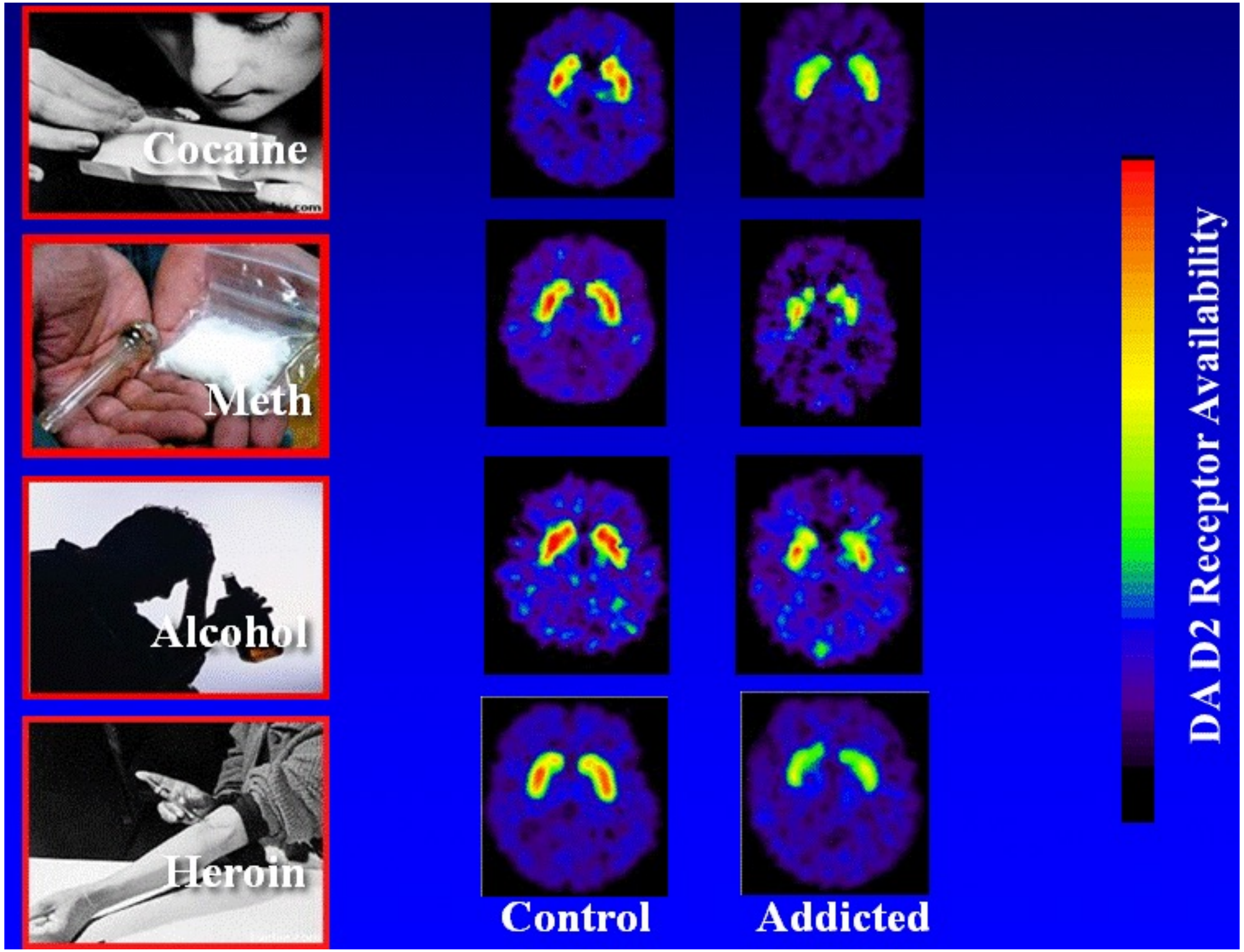
- Very expensive
- Temporally slow
- Poor spatial resolution

BUT

- Useful for targeting specific systems (e.g. DA)

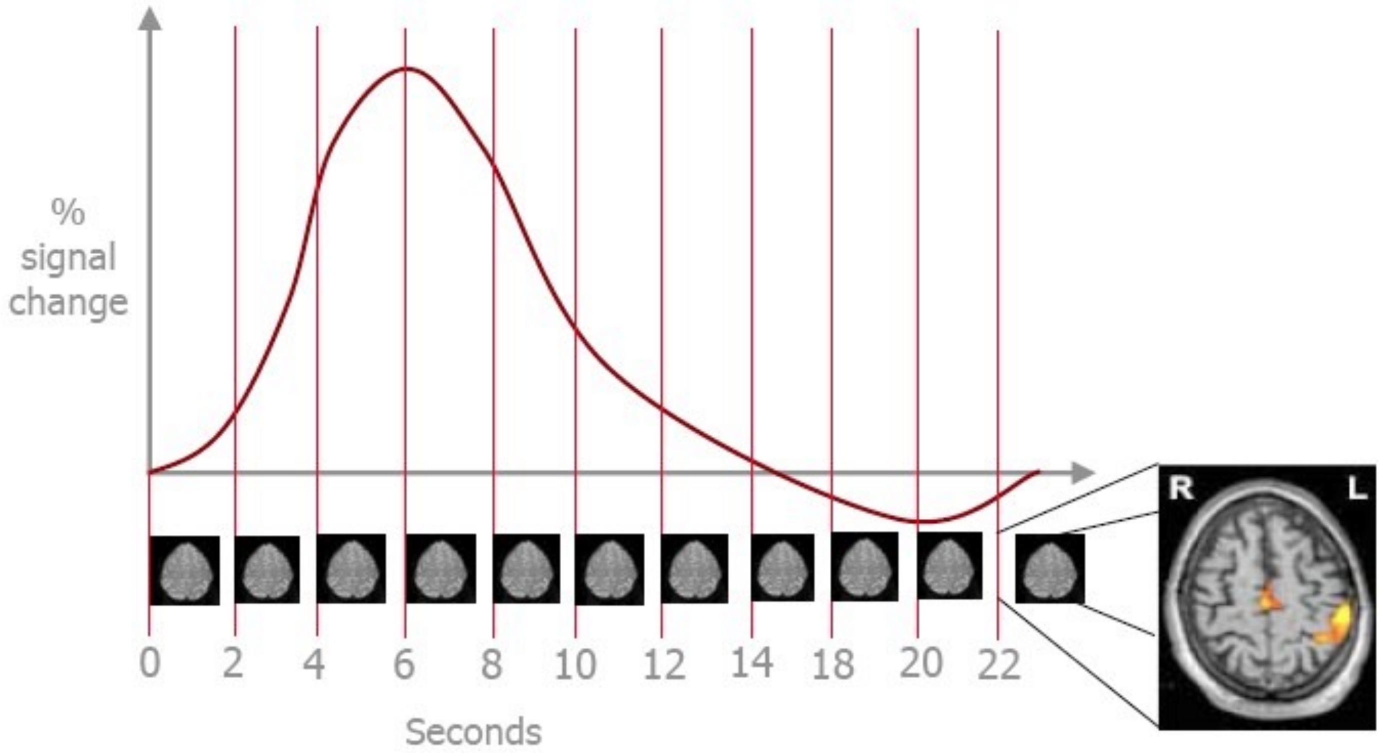


PET: dopamine D_2 receptors decreased by addiction

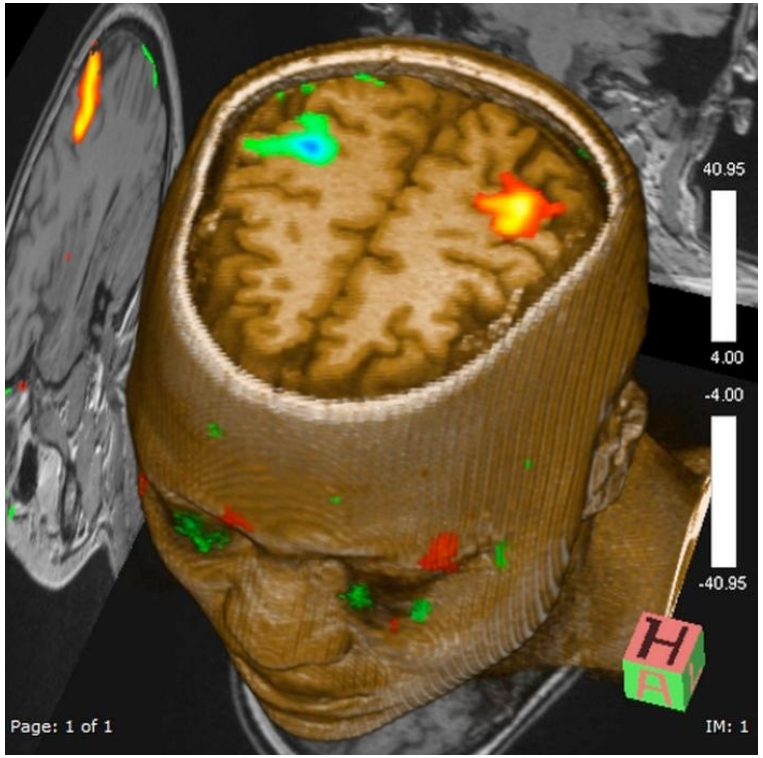


Functional imaging

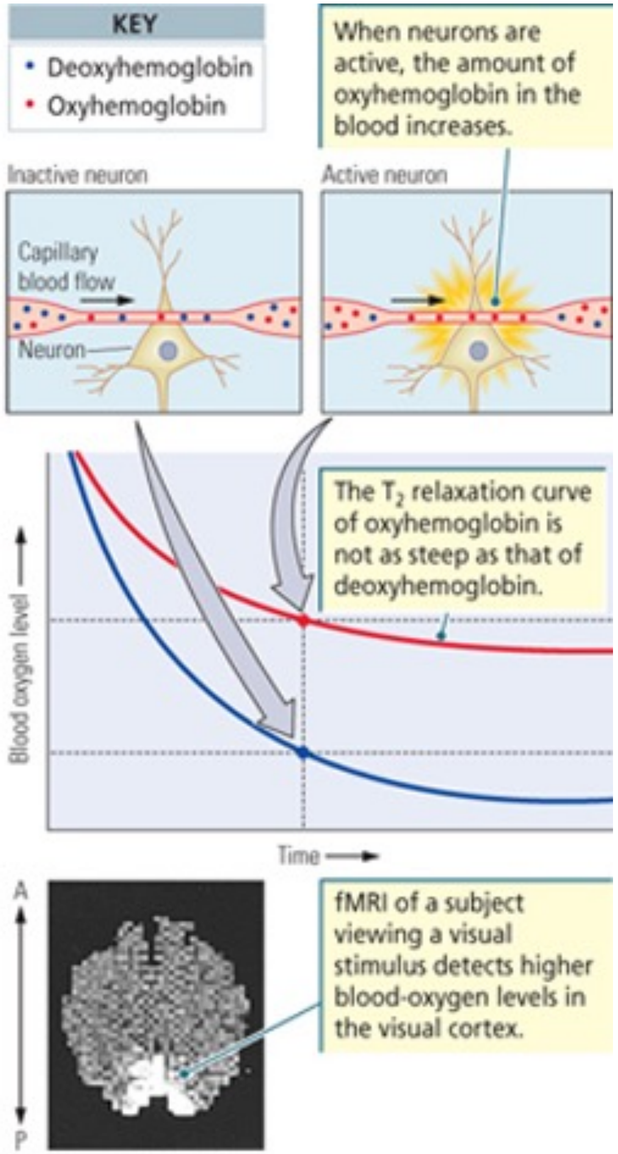
Functional MRI (fMRI): the BOLD response

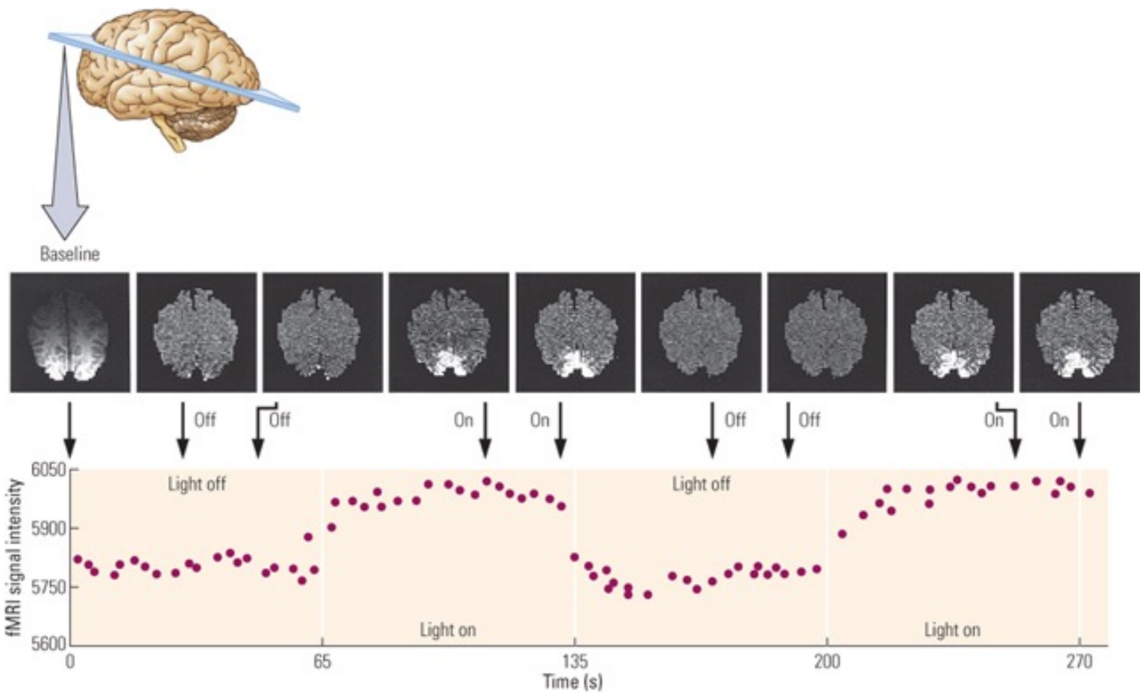


Hemodynamic response

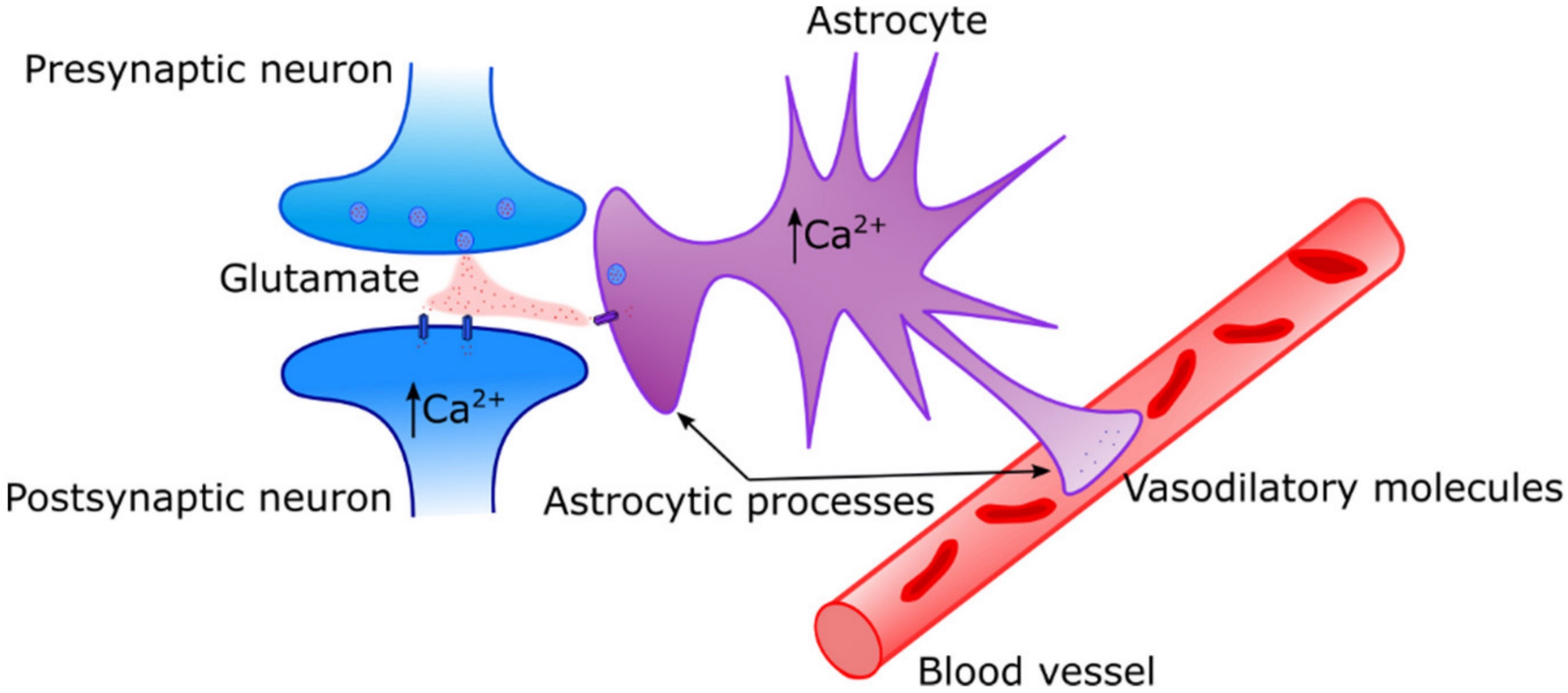


fMRI

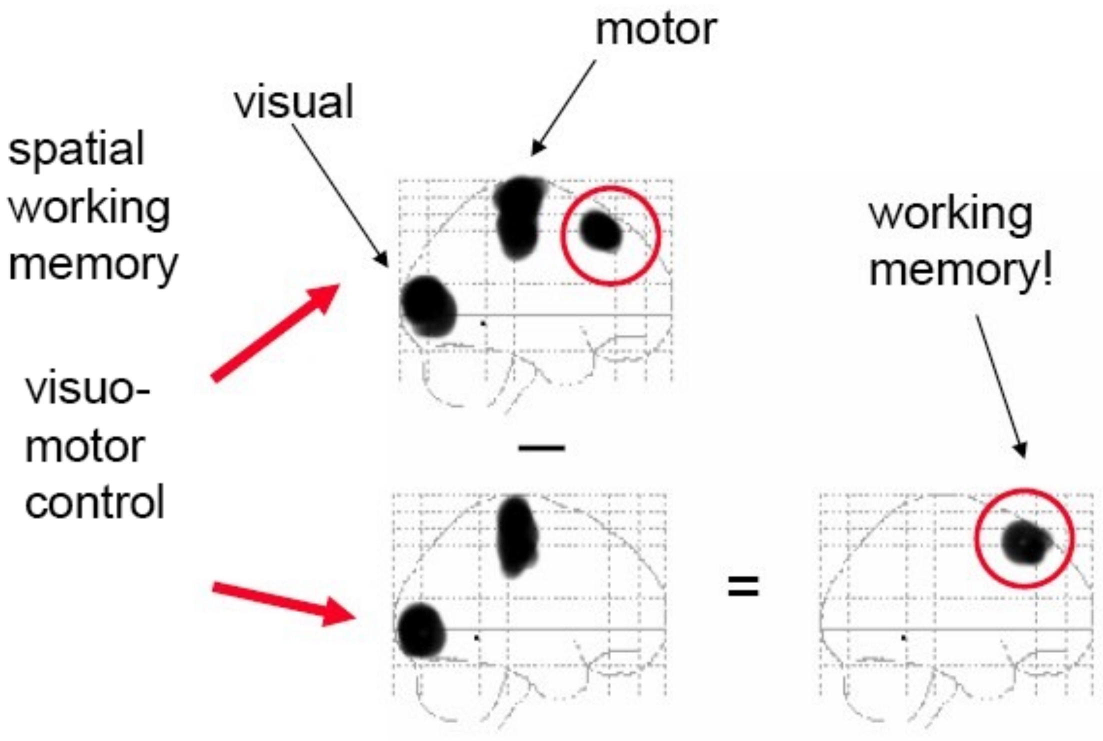

KEY
Deoxyhemoglobin
Oxyhemoglobin
When neurons are active, the amount of oxyhemoglobin in the blood increases.
Inactive neuron
Active neuron
Capillary blood flow
Neuron
The T_2 relaxation curve of oxyhemoglobin is not as steep as that of deoxyhemoglobin.
Blood oxygen level
Time
A
P
fMRI of a subject viewing a visual stimulus detects higher blood-oxygen levels in the visual cortex.


Baseline
Off
Off
On
On
Off
Off
On
On
Light off
Light on
Light off
Light on
fMRI signal intensity
6050
5900
5750
5600
0
65
135
200
270
Time (s)

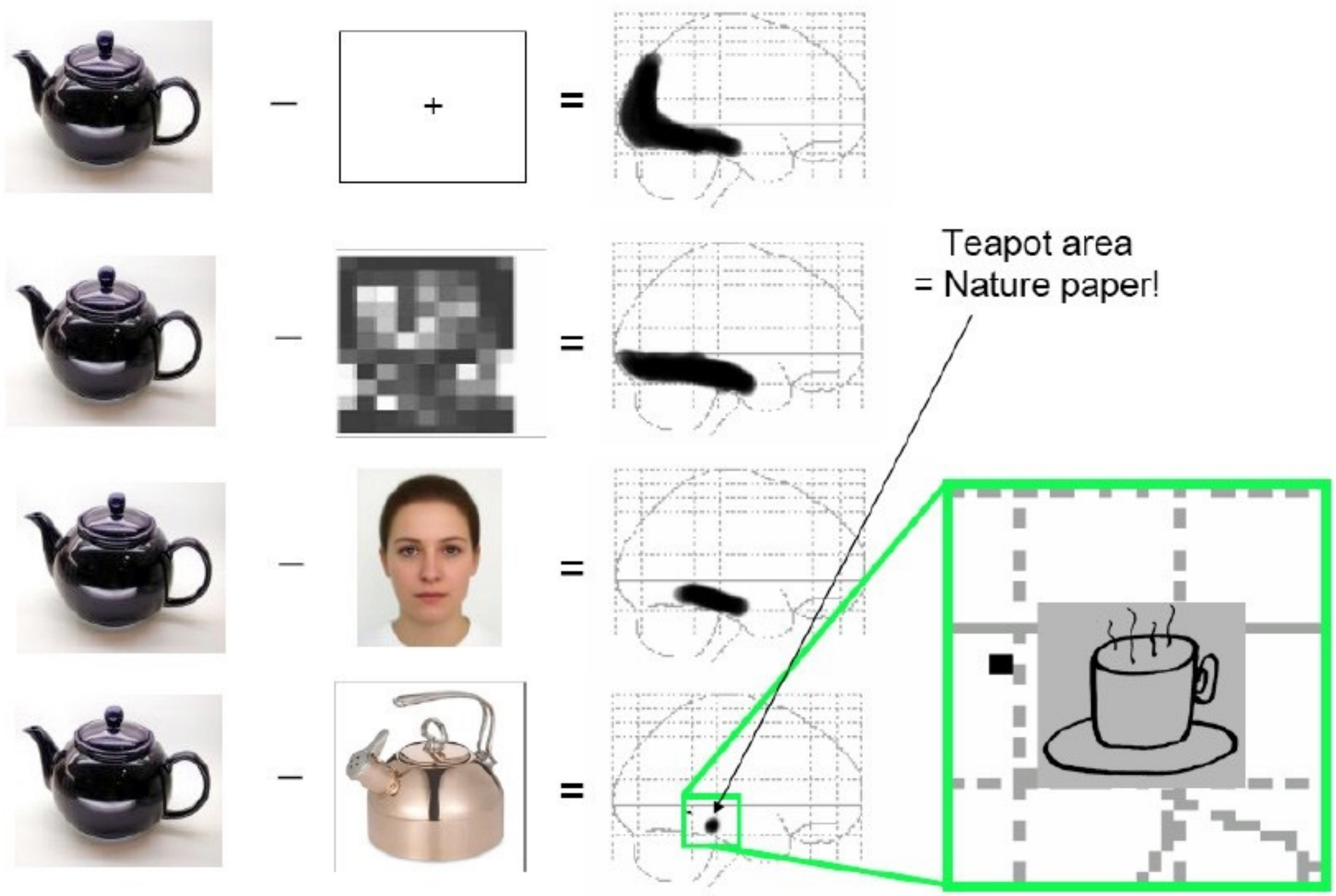
fMRI: BOLD response



Paired Image Subtraction



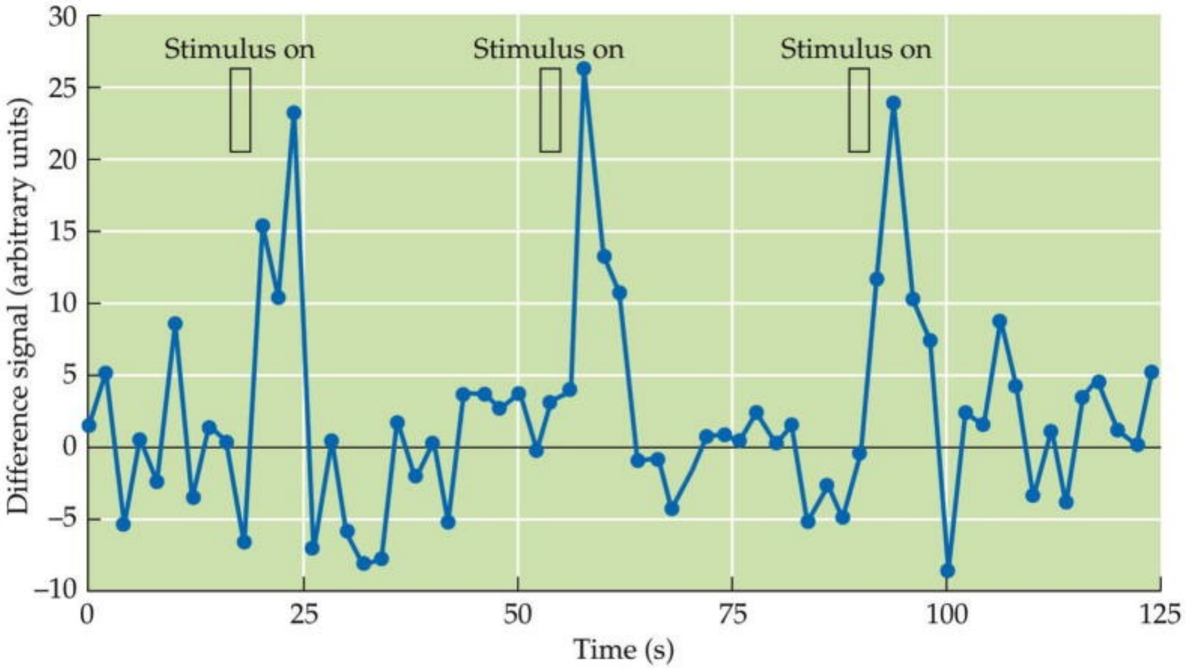
Paired Image Subtraction



The quality of your results depends on the quality of your controls!

Event-related fMRI

Hosking et al. 2017



Huettel 2012,
adapted from Blamire *et al.* 1992

Common in fMRI these days
Allows you to avoid paired image subtraction
Has many of its own challenges (e.g. boredom!)

Problems with interpreting fMRI studies?

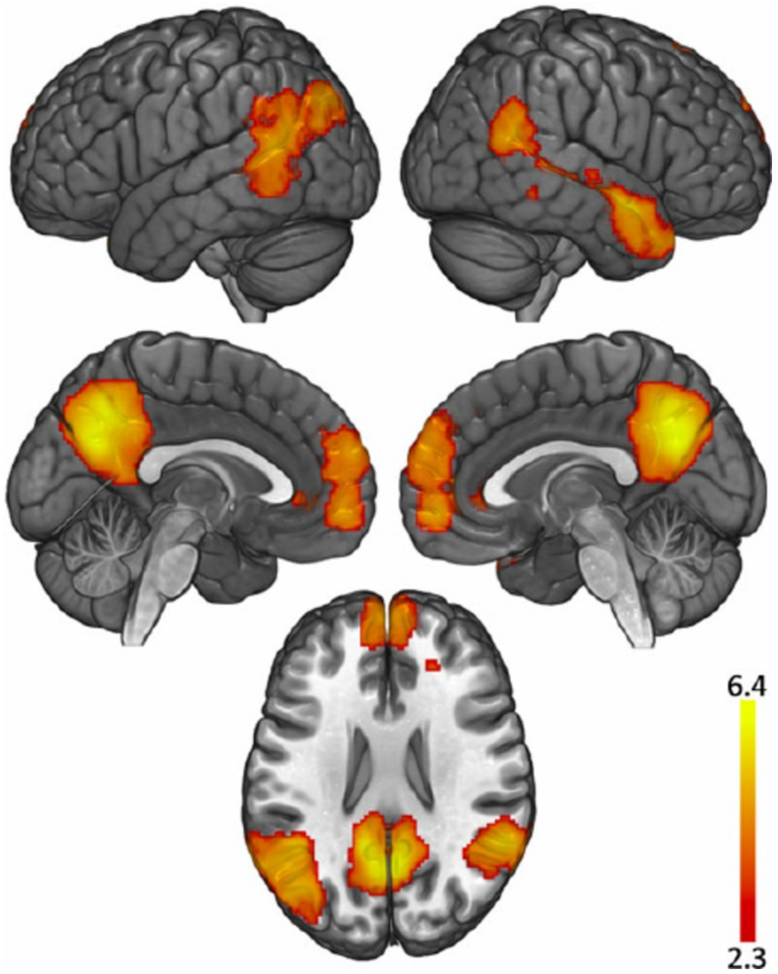
1. Spatial averaging
2. Spatial resolution
3. Temporal resolution
4. Not necessarily necessity
5. Focus on increases in activity

Voxel = 3D pixel

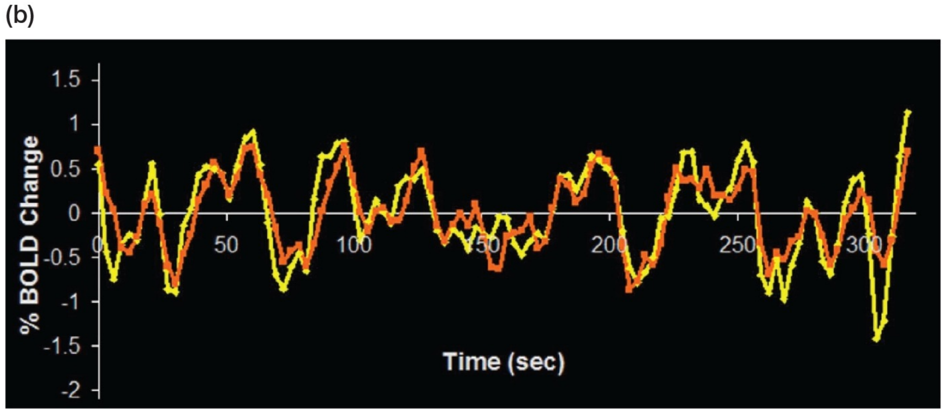
5. Focus on increases in activity: some regions are more active at rest than during task!

The default mode network

mPFC, posterior parietal cortex, PCC,
hipp, lateral temporal cortex

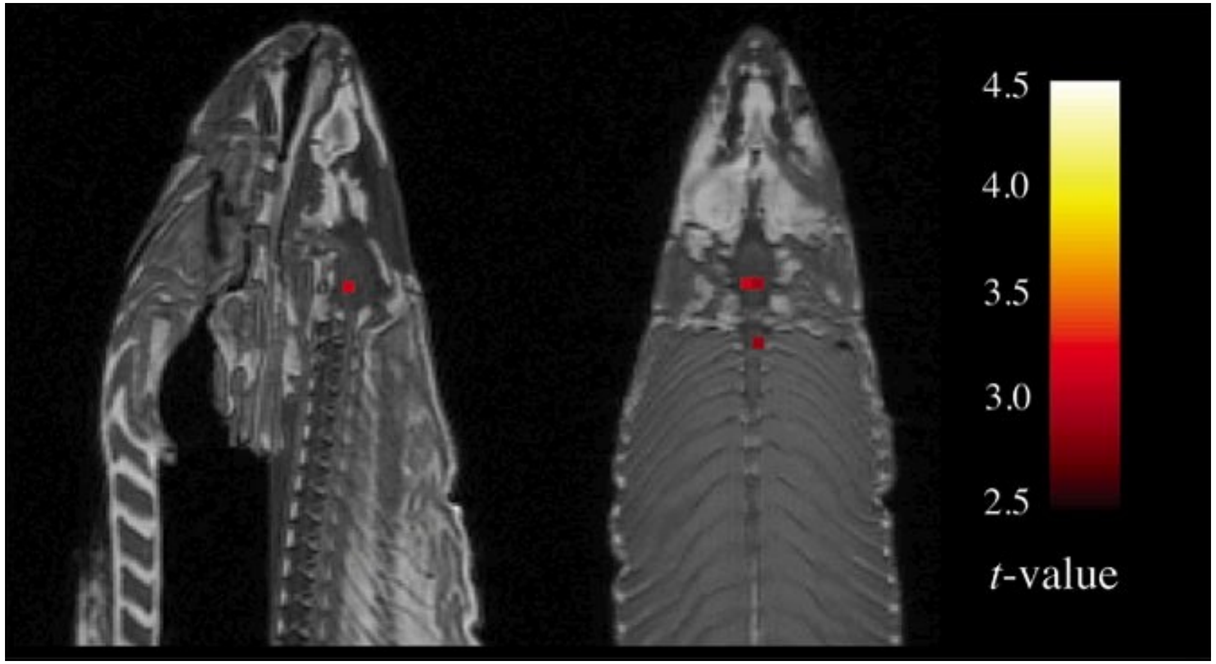


Resting state functional connectivity MRI

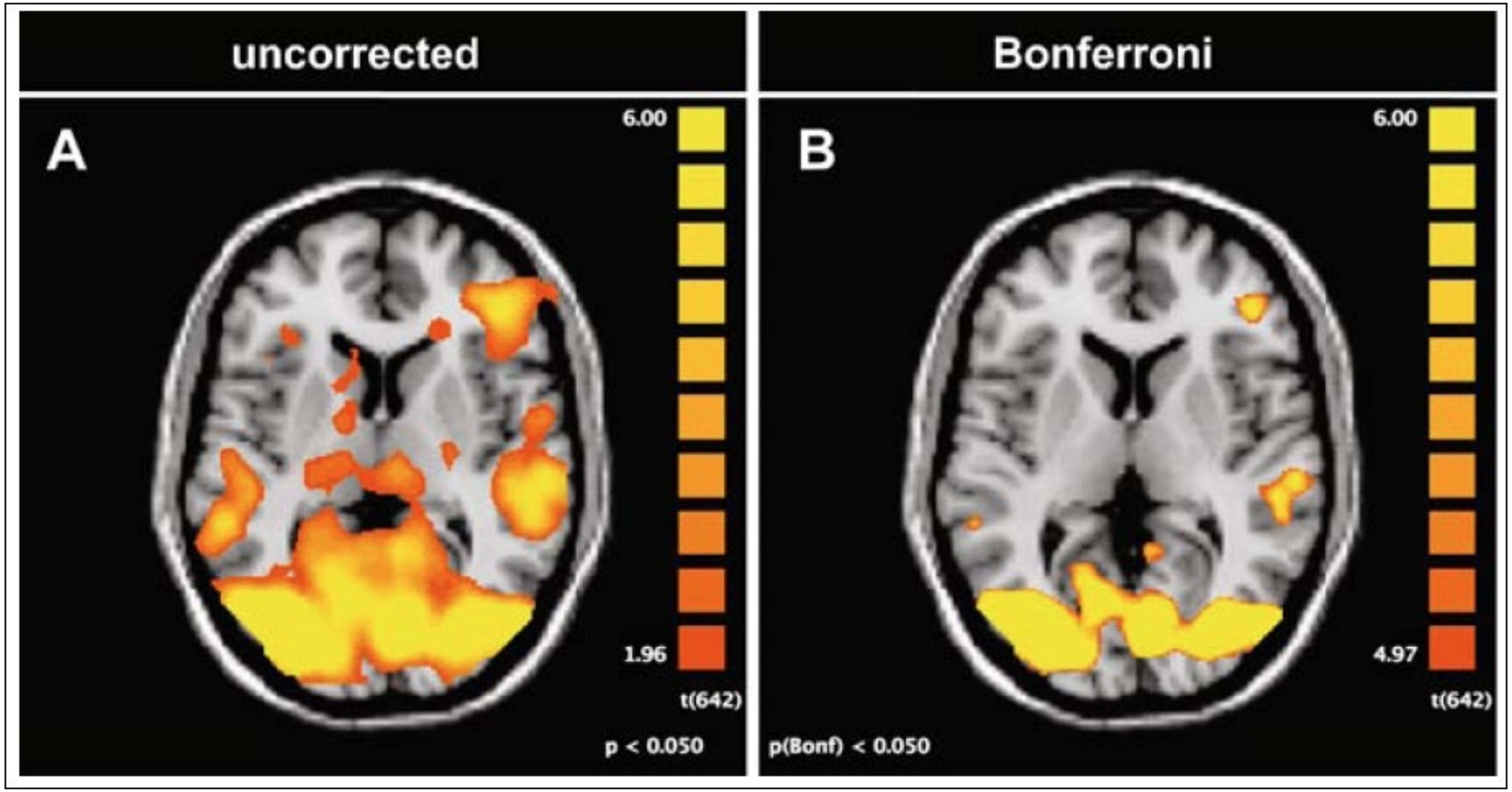


Problems with interpreting fMRI studies?

6. Regional hemodynamics
7. Confounds: anxiety, boredom
8. Drugs
9. Anticipatory hemodynamics
10. Reliability
11. Statistics



11. Statistics

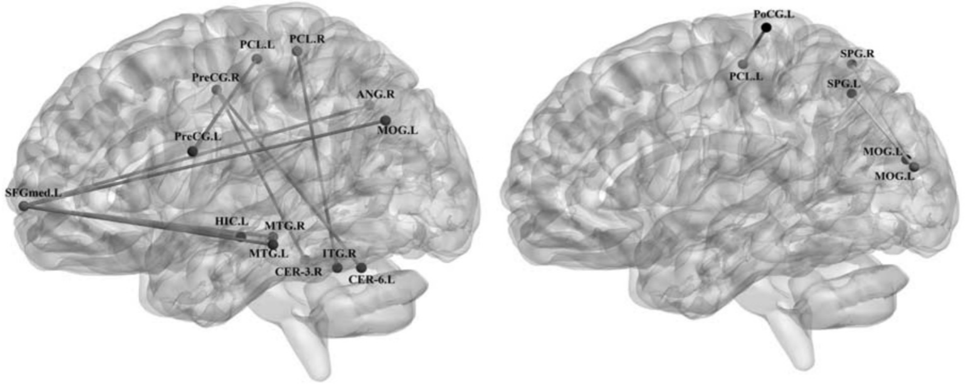


The heavy metal brain?

Altered resting-state functional connectivity of default-mode network and sensorimotor network in heavy metal music lovers

Yan Sun[a,b], Congcong Zhang[a,b], Shuxia Duan[a,b], Xiaoxia Du[c] and Vince D. Calhoun[d,e,f]

The aim of this study was to investigate the spontaneous neural activity and functional connectivity (FC) in heavy metal music lovers (HMML) compared with classical music lovers (CML) during resting state. Forty HMML and 31 CML underwent resting-state functional MRI scans. Fractional amplitude of low-frequency fluctuations (fALFF) and seed-based resting-state FC were computed to explore regional activity and functional integration. A voxel-based two-sample *t*-test was used to test the differences between the two groups. Compared with CML, HMML showed functional alterations: higher fALFF in the right precentral gyrus, the bilateral paracentral lobule, and the left middle occipital gyrus, lower fALFF in the left medial superior frontal gyrus, an altered FC in the default-mode network, lower connectivity between the right precentral gyrus and the left cerebellum-6 and the right cerebellum-3, and an altered FC between the left paracentral lobule and the sensorimotor network, lower in the right paracentral lobule and the right inferior temporal gyrus FC. The results may partly explain the disorders of behavioral and emotional cognition in HMML compared with CML and are consistent with our predictions. These findings may help provide a basic understanding of the potential neural mechanism of HMML. *NeuroReport* 00:000–000



- Poor assumptions?
- Multiple methods is critical

Thinking critically

Choose wisely

Which biopsychology method would you choose to study the following questions, and why?

1. Loss of grey matter in the weeks following a stroke
2. Changes in non-cortical brain activity following a stroke
3. Cortical activity while running on a treadmill
4. The external stimuli and situations in which a neuron fires
5. Changes in protein expression following a neurodegenerative disease (e.g. Alzheimer's, CTE)
6. The role of the hippocampus in spatial learning and navigation.
7. Changes in decision making and motivation following acute and chronic drug use.
8. How we select words from our vocabulary for speaking.
9. The role of monoamine neurotransmitters in motivation.
10. What regions of the motor cortex control what parts of the body.

"Assignment"