Announcements

- Final Exam will be a take-home exam
- Format similar to the short assignment (no multiple choice, etc.)
- Will be handed out at end of last class period (Thursday June 5th)
- Due by 6 pm June 10th (Tuesday)
  - By email or hardcopy

Methods for assessing the brain basis of developmental disorders

Developmental Disorders

- Autism
  - Impaired language; impaired cognition
- Savant syndrome
  - Superior language; impaired cognition
- Specific Language Impairment
  - Impaired language; spared cognition
- Williams syndrome
  - Spared language; impaired cognition

Natural Experiments

Lesions and Disorders

Phrenology: Structure-function correspondence

Gall, Spurzheim; early 19th century

- Key Claim
  - Cognitive functions can be localized to specific brain regions or structures

Problematic Claims

- Size of brain region changes the skull
- Size of brain region correlates with degree of function

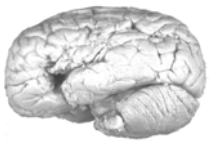
Huge problem:

No theory of Psychology!

Which functions are in the brain?

The Lesion Method

- Brain is damaged following injury or disease
- Which functions are lost, which retained?
- Lost functions necessarily depended on damaged tissue



Leborgne "…tan"

Paul Broca

1861

Caveats

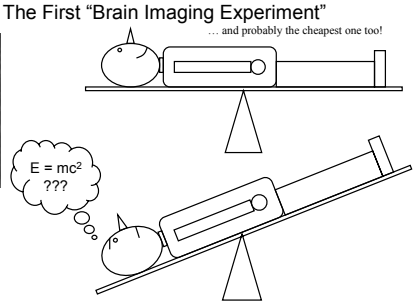
- Size of lesion cannot be controlled
- Location of lesion cannot be controlled
- Compensation may occur

Unnatural experiments

Measuring (intact) brains

The First "Brain Imaging Experiment"

Angelo Mosso
Italian physiologist
(1846-1910)



"[In Mosso's experiments] the subject to be observed lay on a delicately balanced table which could tip downward either at the head or at the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system."
-- William James, *Principles of Psychology* (1890)

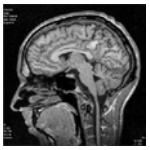
Source: Jody Culham's fMRI for Dummies web site

Spatial Dynamics:

(f)MRI and PET

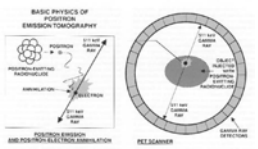
functional Magnetic Resonance Imaging (fMRI)

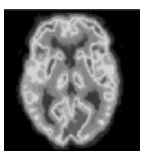
- BOLD signal measures oxygen use in blood; blood flows to active brain regions
- Excellent spatial resolution (~1 mm^3)
- Non-invasive
- Poor temporal resolution; hemodynamic response is slow (peak ~6 seconds)
- Whole brain image takes ~1-4 seconds to acquire
- Dangerous environment
  - strong magnetic field (1.5 or 3 Tesla common for research; earth's magnetic field is 10^{-4} T)
  - superconducting magnet cooled by liquid helium
- Expensive



Positron Emission Tomography (PET)

- Radioactive isotope injected into blood, delivered to active brain regions
- Good spatial resolution (~ 5 mm^3)
- Very flexible; lots of different measurements possible (metabolism, etc.)
- Poor temporal resolution (~10 seconds; 20 minutes)
- Short half life; isotope must be manufactured nearby
- Very invasive; limited testing
- Expensive





Temporal dynamics:

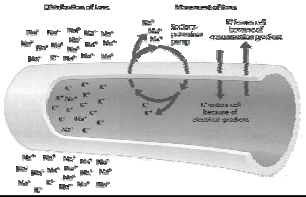
Electricity (EEG) and Magnetism (MEG)

Neurons

- Resting potential
  - Slightly negative
  - -70 mV
  - Sodium ions kept out of cell
- Action potential
  - Ions enter cell
  - Neuron is depolarized (-55 mV)
  - All or nothing response

- Action potential propagates along axon from axon hillock
- Ion exchange at nodes of Ranvier

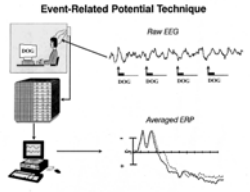
- Current flow inside neuron yields MEG
- Return current of ions outside neuron yields EEG



Event-related potentials (ERP)

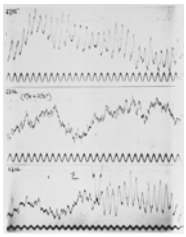
- Summed electrical activity of a large number of neurons
- Measured at scalp (~10 microvolts)
- Excellent temporal resolution (sub-millisecond)
- Non-invasive; cheap, easy to administer

- Poor spatial resolution: Inverse Problem
- Data is noisy



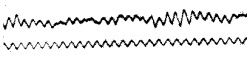
The first EEG recordings

Hans Berger (1873 - 1941)

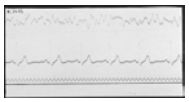


Alpha waves

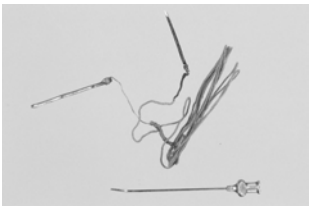
"The electroencephalogram represents a continuous curve with continuous oscillations in which ... one can distinguish larger *first order waves* with an average duration of 90 milliseconds [**Alpha waves**] and smaller *second order waves* of an average duration of 35 milliseconds [**Beta waves**]. The larger deflections measure at most 150 to 200 microvolts...." (*H. Berger, 1929*)



First EEG recorded by Hans Berger, circa 1924



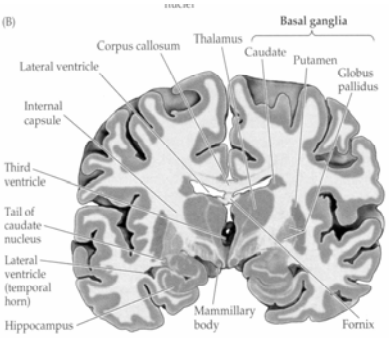
EEG and EKG (electrocardiogram)



Hans Berger's needle electrodes

Lucky us!

EEG is produced



in cortical gray matter

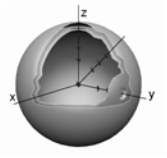
by neurons that have a dipole structure (pyramidal cells) oriented perpendicular to the scalp

when lots of parallel neurons are activated synchronously (via thalamus)

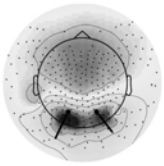
➢EEG does not reflect action potentials!

Poor Spatial Resolution in EEG

- The forward problem:
  - Given one or more dipoles in the brain, calculate the electric field at the scalp
  - Accommodate distortion due to skull, etc.

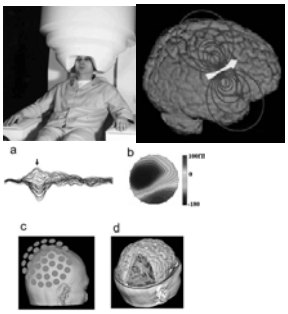


- The inverse problem:
  - For any electric field at the scalp there are an infinite number of possible dipole combinations
  - Possible dipole locations can be estimated by additional information (e.g., MRI, fMRI)



Magneto-encephalography (MEG)

- Magnetic fields produced by electric currents in a wire (axon)
- Measurable from currents parallel to scalp
- Tiny amplitude (10^{-13} Tesla; earth's magnetic field is 10^{-4} T)
- Good temporal resolution (sub-millisecond)
- Non-invasive
- Poor spatial resolution
- Expensive (superconducting SQUID); magnetic shielding required



Subdural Grids

- Grids of electrodes, implanted on the surface of the brain (under the dura)
- Very good spatial resolution (limited by electrode array); millisecond or better temporal resolution
- Very invasive
- Used in epilepsy patients – Is brain function 'normal'?

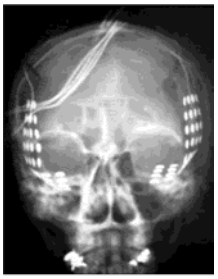
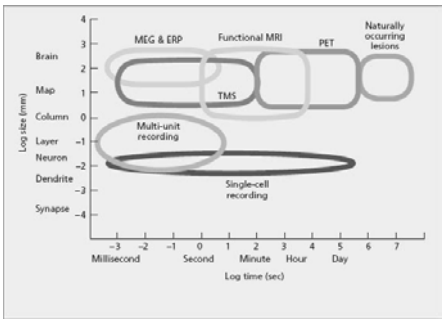


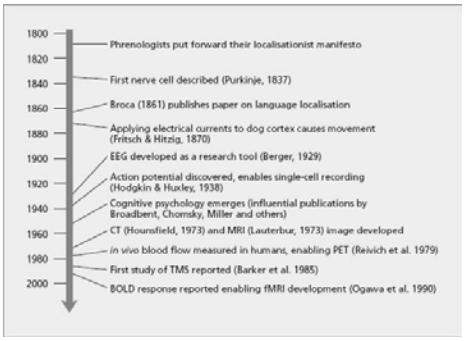
Fig. 1. Skull X-ray showing the typical appearance of the bilaterally implanted grids in group I patients.

Summary of Methods

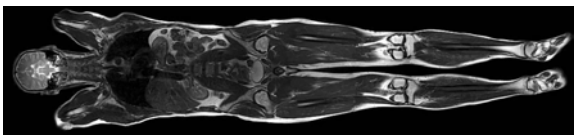


NOTE: subcortical structures measured by fMRI, PET, lesion

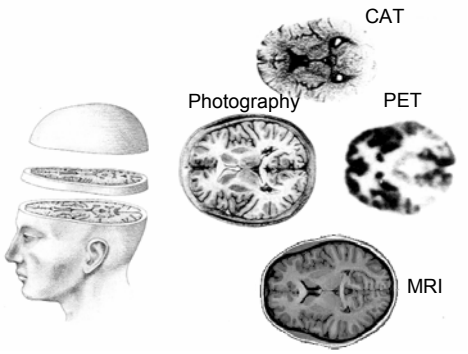
Historical Timeline



Methods: Magnetic Resonance Imaging (MRI)

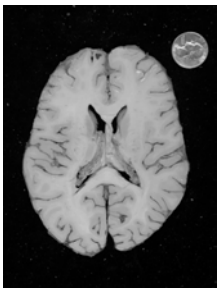


Brain Imaging: Anatomy



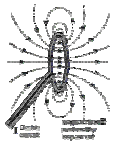
Source: modified from Posner & Raichle, Images of Mind

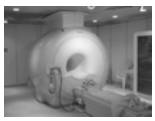
MRI provides near photographic detail with no radiation



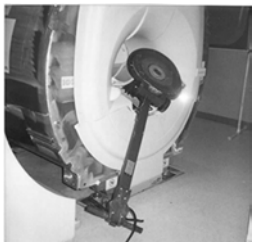
Static magnetic field: B_0

- Superconducting electromagnet cooled with liquid helium
- B_0 is typically 1.5 or 3 Tesla; 7 T or higher is possible
- Earth's magnetic field is 10^{-4} T
- Once powered up, the magnet stays on!



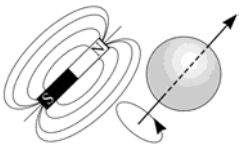


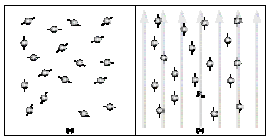
The magnet is always on!



Protons protons everywhere

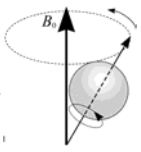
- Spinning protons are like tiny magnets
- B_0 causes proton spins to align with direction of magnetic field





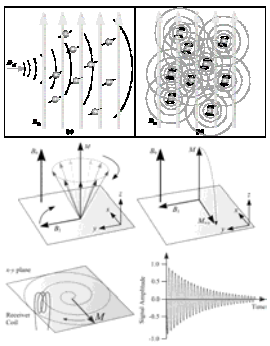
Protons "precess" as they spin within main magnetic field

Precession provides basis for detectable signal

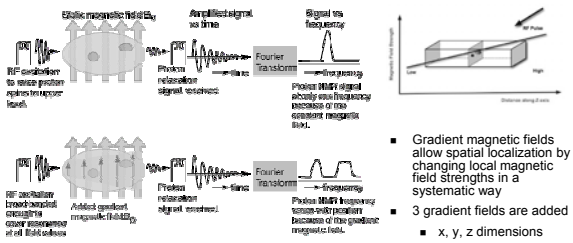


Extracting a signal

- Radio-frequency (rf) pulses at precession frequency knock protons out of alignment
- Protons precess at right angle to receiver rf coil – synchronized precession induces detectable current in receiver coil
- Signal is distorted by local magnetic fields (biological tissues), signal decays (loses synchrony) within about 100 milliseconds
- Protons re-align with main magnetic field within a few seconds



Gradient magnetic fields



- Gradient magnetic fields allow spatial localization by changing local magnetic field strengths in a systematic way
- 3 gradient fields are added
  - x, y, z dimensions

Summary

- Necessary components of an MR machine
  - Superconducting magnet to produce B_0
  - Magnets to produce gradient fields for spatial localization
  - Radio frequency coil (at 90° to B_0)
    - transmitter (to knock protons out of alignment with B_0, generate signal)
    - receiver (to detect signal)

MRI vs. fMRI

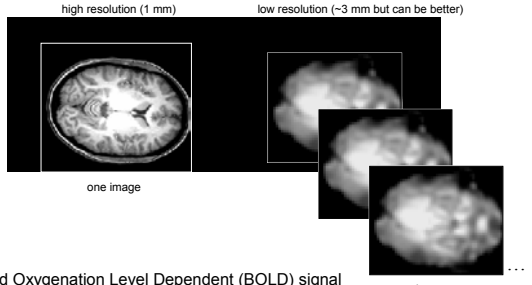
MRI studies brain <u>anatomy</u>.

<u>Functional</u> MRI (fMRI) studies brain <u>function</u>.

Source: Jody Culham's fMRI for Dummies web site

MRI vs. fMRI

high resolution (1 mm) low resolution (~3 mm but can be better)



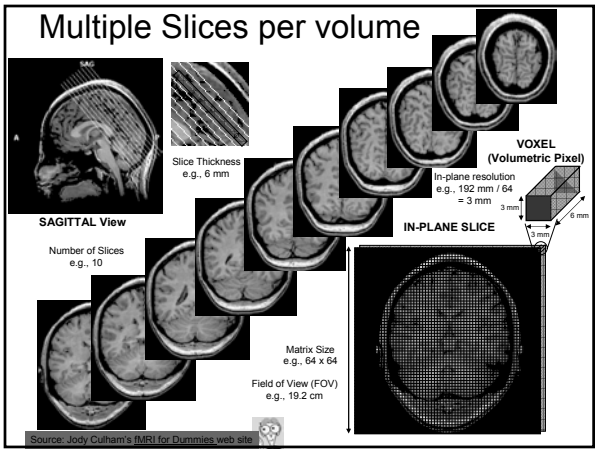
one image

many images
(e.g., every 2 sec for 5 mins)

<u>fMRI</u>
Blood Oxygenation Level Dependent (BOLD) signal
indirect measure of neural activity

Source: Jody Culham's fMRI for Dummies web site

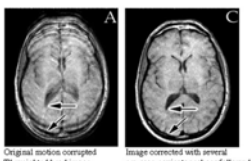
Multiple Slices per volume



Source: Jody Culham's fMRI for Dummies web site

Motion Artifacts

- Translation
  - x,y,z
- Rotation
  - yaw, pitch, roll
- Pulsatile motion
  - Brain is not rigid
- Correction algorithms



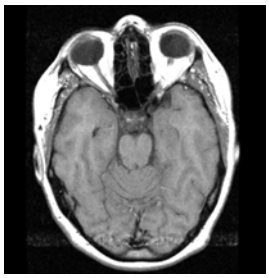
Original motion corrupted T1 weighted head image

Image corrected with several per-scan navigator echoes followed by autocorrection

Voxels are fixed in space. Motion changes the voxel that a volume of tissue contributes to, leading to a blurry picture

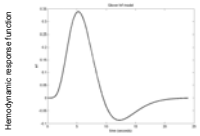
Structural Imaging

- Sources of image contrast
  - # of protons per voxel (volume of tissue)
  - Variation in local magnetic fields changes signal strength
  - Local magnetic field strength affected by chemical composition of tissue in voxel
- Spatial resolution practically limited by time to acquire images; signal to noise ratio (SNR).
- Increased field strength improves SNR, yields better images (1.5 T; 3 T common; 7 T possible)

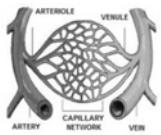


Functional Imaging: BOLD (Blood Oxygen Level Dependent)

- Contrast agents are paramagnetic materials that distort local magnetic fields
- Deoxyhemoglobin is strongly paramagnetic; oxyhemoglobin is not

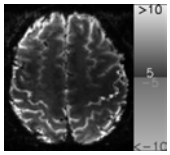


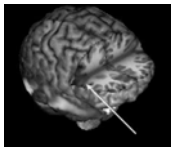
- The BOLD Signal
  - Increased neural activity → increased local blood flow
  - Decreased deoxyhemoglobin in venous blood → uniform local magnetic field strength
  - Change in NMR signal



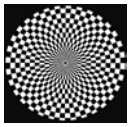
One more time…

- Neurons use oxygen
- Venous blood contains deoxyhemoglobin
- Increased blood flow is excessive (overcompensation)
- Venous blood contains excessive oxyhemoglobin
- Concentration of deoxyhemoglobin goes down
- Decrease of deoxyhemoglobin (paramagnetic contrast agent) makes NMR signal more uniform
- Less distorted local magnetic field leads to increased signal strength (~3% difference)
- Increased signal "lights up" active brain regions

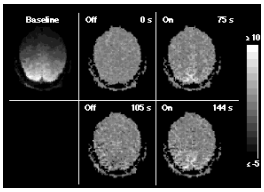




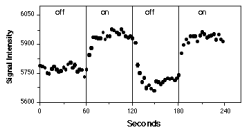
fMRI Activation



Flickering Checkerboard
OFF (60 s) - ON (60 s) -OFF (60 s) - ON (60 s) - OFF (60 s)



Brain Activity



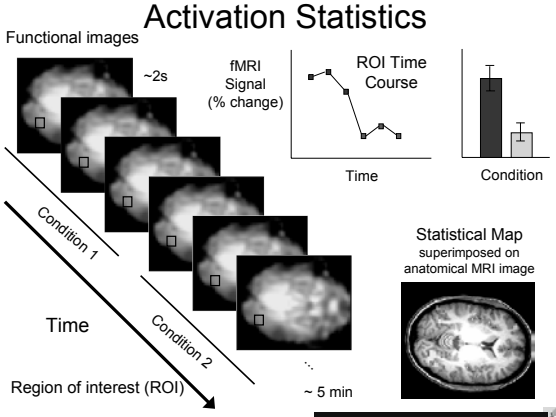
Time ⇨

Source: Kwong et al., 1992

Subtraction and mental processes

- Images of blood flow taken before a task is begun are compared with those obtained when the brain is engaged in that task.
- Investigators refer to these two periods as the control state and the task state.
- Researchers carefully choose each state so as to isolate as best as possible a limited number of mental operations.
- Subtracting blood-flow measurements made in the control state from each task state indicates those parts of the brain active during a particular task.

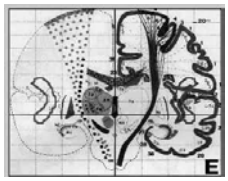
Activation Statistics

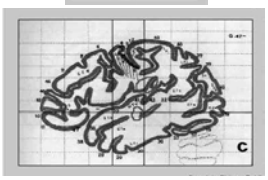


Individuals vs groups

- Talairach atlas

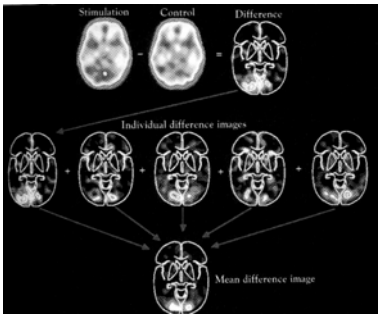
(Talairach and Tournoux, 1988)





Provides standard coordinate system for comparing individual brains, both within and across studies.

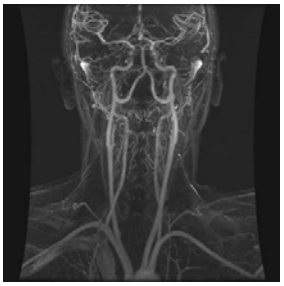
An average brain

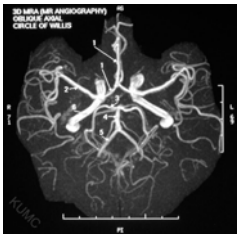


Source: Posner & Raichle, Images of Mind

Additional Uses of MRI

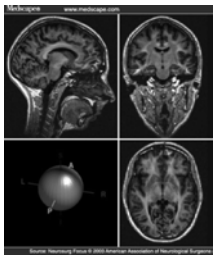
Magnetic Resonance Angiography (MRA)





1. Anterior cerebral artery
2. Middle cerebral artery
3. Posterior cerebral artery
4. Basilar artery
5. Vertebral artery
6. Internal carotid artery

Diffusion Tensor Imaging

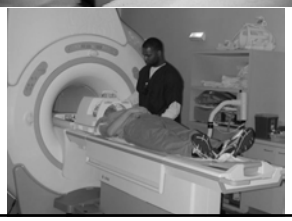


- Diffusion of water in 3d – white matter tractography – water diffusion follows axon bundles

MRI Safety Issues

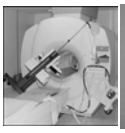
- Follow standard safety procedures (American College of Radiology)
- Ferromagnetic objects (containing iron) will move to the center of the magnet
- Implanted metallic objects may shift position
- Currents may be induced in loops of wire, leading to burns

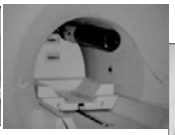
➢ MRI is very, very safe, when proper safety procedures are followed!



"OK, Mrs. Dunn. We'll slide you in there, scan your brain, and see if we can find out why you've been having these spells of claustrophobia."

Accidents can happen





Oops