Recording activity in intact human brain

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Objectives:
- review available recording methods
  EEG and MEG
  single unit recording
  PET
  fMRI
- discuss strengths and limitations of fMRI in particular

Animal studies can yield information on sensory and motor systems, and even simple memory tasks, but to learn about more complex mental states we must study the human brain. Above all techniques must be safe.

EEG and MEG

Electroencephalogram (EEG) and magnetoencephalogram (MEG) are safe and simple, but can only identify mass action of many neurons and have low spatial resolution. EEG also clinically useful for identifying stages of sleep, diagnosing brain death, etc.
Electrodes for single unit recordings in intact human brain

Traditional physiology is possible using patients in mid-brain surgery, and has yielded exciting results, but it is difficult to recruit subjects and they will all have disease states.

Positron emission tomography: PET

— tracks gamma rays from a radionuclide tracer
— different tracers can scan for glucose metabolism, neurotransmitter binding, etc.
— poor spatial and temporal resolution, requires exposing subject to tracers, tracers difficult to work with

Functional magnetic resonance imaging: fMRI

Nuclear magnetic resonance (NMR)

When nuclei are immersed in a stable magnetic field, those nuclei with a non-zero spin have a magnetic moment and tend to align themselves with the static field. As the nuclei are exposed to a second, oscillating field (RF), when the oscillating field changes the nuclei are perturbed and then relax back into alignment. During relaxation, they emit RF radiation characteristic of the nuclei and their environment.
Static magnetic resonance imaging (MRI)

MRI at the resonance frequency for $^1$H in water to take static 3-D pictures of living organism.

Different soft tissues have sufficiently large differences in relaxation rates that the algorithm can distinguish between them.

BOLD fMRI

Blood flows rapidly to brain areas with increased energy use. The blood oxygenation level dependent (BOLD) contrast measures the oxygenation level of hemoglobin and acts as a surrogate signal for neuronal activity.

First fMRI without exogenous contrast agents 1991.

So where do the colored blobs come from?

Blood flows rapidly to brain areas with increased energy use. The blood oxygenation level dependent (BOLD) contrast measures the oxygenation level of hemoglobin and acts as a surrogate signal for neuronal activity.
Six painful problems for fMRI:

1. Indirect measurement of neuronal activity
2. Low temporal resolution
3. Low spatial resolution
4. Comparisons between individuals
5. Comparisons over time
6. Statistics and analysis

Problem 1: fMRI is an indirect measurement of neuronal activity

All fMRI operates on the assumption that the brain is organized in functional modules that map onto brain regions.

One voxel typically contains millions of neurons, billions of synapses, and kilometers of axons and dendrites.

Increased neuronal activity does not necessarily represent increased net excitatory activity in that brain area.

Problem 2: fMRI has low temporal resolution

fMRI is only as fast as blood flow—hemodynamic delay of seconds.

Problem 3: fMRI has low spatial resolution

It depends on the strength on the magnetic field, with a minimum of about 1 mm for most applications (~0.5 mm has been claimed). Lowest magnetic field strength for fMRI: ~1.5 T, which yields about 5 mm resolution. Human study maximum is 4 T. Smoothing further reduces resolution.
Problem 4: Comparisons between individuals are challenging

fMRI data must be transformed to map onto an ideal brain to compensate for differences in anatomy. Individual differences in anatomy and fMRI activity do not necessarily translate into differences in function; individual variation is high, and even gross abnormalities can actually be compensatory.

Problem 5: Comparisons over time are very challenging

The test-retest reliability of fMRI is fairly low—the average overlap between single tests of the same subject 1 hour apart is about 33%, and gets lower the longer the interval. Why?

- minimal number of scans, low field strength, poorly optimized equipment lead to high SNR (flexible)
- neuromodulation and attention have strong BOLD signal (not so flexible)

Reliability depends greatly on the experimental design; motor and sensory tasks are the most repeatable, cognitive and emotional least

Aging and illness can effect numerous functional and anatomical changes

Problem 6: Statistical models are challenging

The statistics involved in large data sets can become prohibitively complex, and spurious correlations can crop up in studies even from experienced investigators.

Generally, results are presented as a voxelwise level of significance

Univariate: compare a particular voxel between trials or individuals
Multivariate: compare voxels recorded at many locations simultaneously

These problems are NOT specific to fMRI studies—they arise in many data-heavy fields.

Solving problem 1 [proxy signal]: Decoding— a better way to use fMRI for “mind reading”

Earlier fMRI strategy: simple subtraction method

Benetsev et al. 2009

Dotton
Emerald Nuts
Newer strategy: analyze many more voxels, try to identify widely distributed representations of stimuli.

Solving problem 1 (proxy signal): Decoding—a better way to use fMRI for “mind reading”

Earlier fMRI strategy: simple subtraction method

Most recent decoding strategies can partially reconstruct images shown to subjects, predict decision making, and predict whether a subject will believe a statement with above-chance accuracy.

Basic problem for all neuroscience: it’s difficult to study any neural activity without either a clear input (sensory) or output (motor).

Background activity is extremely variable for all types of tasks, but is particular problem for more complex and abstract tasks.

Is there any way to help control for background variability?

Use the physiological state of sleep to create a control background activity in the brain.

Can’t perform tasks while you’re asleep, but you can dream.
Solving problem 5 (retest reliability): controlling background

Apply multivariate decoder to same sleep fMRI scans, give a yes/no answer as to whether a particular synset is present.

It’s a very impressive leap for fMRI, but as a mind-reading technique it’s not very effective.

Six painful problems for fMRI: Are we any closer to solving them?

1. Indirect measurement of neuronal activity  Some progress
2. Low temporal resolution  NO
3. Low spatial resolution  Some progress, may be nearing the wall
4. Comparisons between individuals  NO
5. Comparisons over time  Some progress
6. Statistics and analysis  Considerable progress
Summary

-- there are multiple techniques for studying activity in the human brain, all of which have significant limitations
-- applying the right technique is critical for success
-- fMRI studies require the best experimental design to maximize reliability and reproducibility