Imaging Brain Structure and Function

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Why image the brain?

• What’s wrong? (Medical diagnosis)
• How does it work? (Neuroscience)
• To aid intervention (Medical treatment, Engineering)
Why is the brain hard to image?

• Different soft tissues (gray, white) give low contrast to x-rays
• Cerebral anatomy is 3D complex and variable
• Neurophysiological processes must be imaged indirectly through their coupled vascular and metabolic effects
• Much of the organization of the brain is still poorly understood.
• Cerebral functional zones are defined by microscopic features that can’t be imaged directly
Digital image paradigm

• Images are matrices of values of a physical or physiological parameter, extended over an anatomic space.
• The parameter is not derived “directly” from hardware sensors, but by post-acquisition computation.
• Images may be inputs to further workflow.

Paradoxically, imaging is an abstract concept
Outline

• The brain
• Brain imaging modalities
• Standard anatomical space
• Image processing
The brain is an organ
Sulci and Gyri of the Cerebral Cortex
Cortical thickness

Freesurfer, CARET
Brodmann’s cytoarchitectonic map (1909)
From Amunts et al
Julich cytoarchitectonic map (2009)
Xray Computed Tomography
Tissue vs. Bone Windows

Hounsfield Number – radiodensity
Computed tomography

- First tomographic anatomic imaging technique
- Modest soft tissue contrast
- Contrast agent (iodinated) already existed
- Good sensitivity to pathology, esp. blood
- Good resolution of bony structures
- Rapid (good throughput, low sensitivity to motion)

- Finds uses as a first-line emergency technique
- Integrated with PET for attenuation correction and anatomic image fusion
- Used very extensively in body imaging
Intracerebral hypertensive hemorrhage
In theory, metabolic mapping techniques can resolve cortical processes at the level of cortical columns.

2-deoxyglucose: visual stim in cats
Positron Emission Tomography (PET)

Images of physiological parameters are inferred from the distribution of positron-emitting radiopharmaceuticals.
Positron emission
PET detectors
$^{18}\text{F}]\text{Fluorodeoxyglucose}\ \text{PET}$
PET

- Physiologically distributed signal
- Unrivaled sensitivity
- A medical procedure with ionizing radiation
- Requires radionuclide source (cyclotron) and radiochemistry facilities
- Tracers exist for tissue metabolism (18F-FDG), blood flow (15O-water), DNA synthesis (18F-FLT), Alzheimer disease proteins, and more.
BRAIN IMAGING OF ALZHEIMER’S DISEASE

**AMYLOID PET SCAN**
- Detects amyloid plaques
- Stereotyped distribution
- Leads symptoms by 15 years
- Doesn’t change over time
- Use: to certify diagnosis
- Spinal fluid is an alternative.

**TAU PET SCAN**
- Detects tau tangles
- Variable distribution
- Correlates well with symptoms
- Tracks advance of disease
- Use: to delineate disease impact
- To track treatment
Magnetic Resonance Imaging (MRI)
MRI

• Water molecules have a natural frequency at which they can accept and radiate energy.

• More precisely, the hydrogen nuclei have a quantum mechanical property called spin angular momentum.

• The spin states of hydrogen nuclei diverge in energy level in the presence of a magnetic field.

• Water protons absorb or give off energy to move between these energy levels, at the natural frequency, the Larmor frequency, which is a function of the magnetic field strength.
In a magnetic field, protons precess at a natural frequency. Energy can go in or out of this system *only* at this frequency.
Excitation

• Radiofrequency energy at the Larmor frequency transfers to the water protons of the system.

• This does two things:
  – Introduces a transverse component to the magnetization
  – Synchronizes the precession of the protons

• When the pulse of RF input stops, the system (water in the magnet) will radiate radiofrequency energy for a little while
Relaxation: T1, T2, T2*

• With time (described by T1) the excited dipoles will relax back into alignment with the field.

• Before that happens, their precession will get out of phase (described by T2) and no more signal will be available.

• But even before that, local imperfections in the field will probably cause even faster dephasing (described by T2*).
T1 relaxation occurs at different rates in different tissues

• T1 relaxation is slowest in a homogeneous sample of water (e.g. in CSF)
• T1 relaxation is faster in lipid-rich white matter than in gray matter
• Differential relaxation is the key to tissue contrast in MRI
Together, the values of TR and TE emphasize different tissue parameters.

**T1**
- TR = 300 msec
- TE = 20 msec

**T2**
- TR = 3000 msec
- TE = 120 msec

**PD**
- TR = 3000 msec
- TE = 20 msec

A **short** TR and **short** TE emphasizes T1 contrast.

A **long** TR and **long** TE emphasizes T2 contrast.

A **long** TR and **short** TE emphasizes proton density contrast.
FLAIR: FLuid-Attenuated Inversion Recovery
– T2 weighting with black spinal fluid
The MRI signal is rich

- Proton density
- Relaxation times (T1, T2)
- Magnetic field distortion (T2*)
- Flow
- Diffusion
- Chemical shift
- Magnetization transfer
- .......
Magnetic resonance angiography
“MRA”
The “economy” of MRI

• In MRI signal is the sum of the longitudinal magnetization of the protons in the field of view
• This is a like fixed budget, that can be used more or less efficiently, and can be spent to obtain some combination of:
  – Better spatial resolution
  – Better signal to noise ratio (SNR)
  – Reduced imaging time
• There are always trade-offs!
• Advances in MRI are often in the form of a smarter pulse sequence.
Efficient pulse sequences

- Maximize the amount of time spent listening for the signal
- Maximize the number of protons in the sample that are being put to work at any one time
- Optimize the relationship between TR and TE to maximize signal
- We use two efficient sequences extensively: MP-RAGE and EPI GRE fMRI
Diffusion Tensor Imaging
Diffusion

Random “walk” of the water molecular also known as “Brownian motion”

Isotropic Diffusion

Anisotropic Diffusion

Ellipsoid = Probability of Diffusion Distribution
Diffusion eigenvectors

Diagonalization of this tensor provides three eigenvectors \((ev_1, ev_2\) and \(ev_3)\) with three corresponding eigenvalues \((\lambda_1, \lambda_2\) and \(\lambda_3)\).
Diffusion Tensor Images

T2W

Trace (D)
(Amount of Diffusion)

Anisotropy
(White Matter)

Orientation
of WM
Diffusion imaging

• Parameters neurologists are used to seeing
  – Diffusion-weighted image
  – Apparent diffusion coefficient - ADC

• Parameters neuroscientists are used to seeing
  – Diffusion fractional anisotropy – FA
    A measure of how constrained water is to diffuse in only certain directions
  – Diffusion principal eigenvector
    The axis along which water diffuses most freely
DTI Tract Tracing
In vivo Connectivity-based Cortex Parcellation

1. Preprocess DWI
2. Model Diffusivity
3. Compute and cluster tractograms

Diagram showing brain regions and connectivity.
Functional Magnetic Resonance Imaging (fMRI)
Physiological basis of fMRI

Brain activity is imaged *indirectly*, through parameters related to metabolic substrate delivery.
Neurovascular coupling

Synaptic electrochemical activity

*DEPENS ON*

Maintenance of membrane potentials

*WHICHE DEPENS ON*

Metabolism of glucose

*WHICHE DEPENS ON*

Substrate delivery via blood flow
Basis of fMRI signal

Neural Activity → Metabolism → Blood Flow → dHb → T²* → MR Signal

Hemodynamic Response Function (HRF)

Blood Oxygenation Dependent Signal

“BOLD”
HRF sums linearly over trials

A. Dale and R. Buckner
Hum Brain Mapp 5:329
1997
Activation of the anterior temporal lobes during listening to discourse.
Event-Related Design

MRI signal

Time, seconds
Activation of hippocampus during successful memory encoding and retrieval
Two fMRI paradigms

• Activation paradigm
  – Signal model: predicted BOLD timecourse

• Functional connectivity paradigm
  – Signal model: correlated signal timecourses
Finger tapping

Resting State Paradigm

Biswal et al., 1997
Early visual network

Ventral visual network

Auditory network

Motor network

Default mode network

Salience network

R dorsal attention network

L dorsal attention network

Damoiseaux et al 2006
“Default” Mode Network

Relevance to adaptive behavior

Deactivation DMN

Activation DAN

Relevance to disease

Raichle & Mintun, 2007
Summary: functional connectivity paradigm

- BOLD fluctuations formerly thought to be “noise” are correlated across distant sites.
- Analysis of functional connectivity “at rest” identifies consistent “intrinsic networks”
- Functional connectivity is grounded in anatomic connectivity
- Intrinsic networks may reflect a fundamental level of large-scale physiologic organization
Anchoring standard space
Anchoring standard space

The brain “equator” is the intercommisural line.
Talairach Space
Talairach Space
Montreal Neurological Institute (MNI) space
Voxel-based morphometry
Limits on interpretation of spatial normalization

• Anatomic variability in Talairach space
  – 1.5 cm

• Irreducible cortical variability
  – This variability is itself variable
  – Cytoarchitecture adds another layer of variability

• Not always easy to assign results to one location
  – Local maximum of statistic field, vs center of mass
  – Extent-based statistics vs Magnitude-based statistics

• fMRI data are typically smoothed for SNR reasons
fMRI Data Post-Processing

- Image Acquisition
  - Motion correction
  - Anatomic alignment
  - Intensity normalization

- Physiologic data acquisition
  - Stimulus recording
  - Convolution w/ HRF (EV)

- General linear model
  - Multiple linear regression

- Test statistics
  - Thresholding/inference
  - Interpretation
fMRI time series

MR signal

time
fMRI signal reflects multiple simultaneous effects

• Task
• Physiologic fluctuations
  – Cardiac pulsatility
  – Respiratory effects
  – CSF flow/pulsation
• Head motion/spin history
• Slow drifts
• Thermal noise
Statistical analysis

- Problem: at each voxel, estimate the task effect in the presence of other effects
- Technique: multiple linear regression supported by the general linear model:

\[ Y = \beta_1 X_1 + \beta_2 X_2 + \ldots + \varepsilon \]

- The task effect is estimated by regression coefficient (\( \beta \)) and tested with a \( t \) statistic
Activation of the anterior temporal lobes during listening to discourse.
Summing Up

• MRI approaches to brain structure and function continue to diversify and become more powerful, driven mostly by conceptual and software innovation.
• Multispectral/multimodal approaches are now common, clinically and in research.
• Imaging approaches are beginning to analyze brain activity in terms of natural systems structure (columns, fields, large scale systems)
• Most of the techniques have not (YET) found their way into clinical application
Questions?